

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
4 March 2004 (04.03.2004)

PCT

(10) International Publication Number
WO 2004/017974 A1

(51) International Patent Classification⁷: **A61K 31/502**,
31/50, C07D 401/04, 401/14, 405/14, A61P 11/00

(21) International Application Number:
PCT/EP2003/008724

(22) International Filing Date: 6 August 2003 (06.08.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
02017977.6 10 August 2002 (10.08.2002) EP

(71) Applicant (for all designated States except US): **ALTANA
PHARMA AG** [DE/DE]; Byk-Gulden-Str. 2, 78467 Kon-
stanz (DE).

(72) Inventor (for AE, AL, AM, AT, AU, AZ, BA, BE, BG, BR,
BY, CA, CH, CN, CO, CY, CZ, DE, DK, DZ, EC, EE, ES, FI,
FR, GB, GE, GR, HR, HU, ID, IE, IL, IN, IS, IT, JP, KG, KR,
KZ, LT, LU, LV, MA, MC, MD, MK, MX, NL, NO, NZ, PH,
PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TN, TR, UA, VN,
YU, ZA, ZW only): **STERK, Geert, Jan**; Stadhouderslaan
38, NL-3583 JJ Utrecht (NL).

(72) Inventors (for AE, AL, AM, AT, AU, AZ, BA, BE, BG, BR,
BY, CH, CN, CO, CY, CZ, DE, DK, DZ, EC, EE, ES, FI, FR,
GB, GE, GR, HR, HU, ID, IE, IL, IN, IS, IT, JP, KG, KR,
KZ, LT, LU, LV, MA, MC, MD, MK, MX, NL, NO, NZ, PL, PT,
PT, RO, RU, SE, SG, SI, SK, TJ, TM, TN, TR, UA, VN, YU,
ZA, ZW only): **HATZELMANN, Armin**; Alter Wall 3,
78467 Konstanz (DE). **BARSIG, Johannes**; Bleichenweg
11, 78467 Konstanz (DE).

(72) Inventor (for AE, AL, AM, AT, AU, AZ, BA, BE, BG, BR,
BY, CH, CN, CO, CY, CZ, DE, DK, DZ, EC, EE, ES, FI, FR,
GB, GE, GR, HR, HU, ID, IE, IL, IN, IS, IT, JP, KG, KR, KZ,
LT, LU, LV, MA, MC, MD, MK, MX, NL, NO, NZ, PL, PT,
RO, RU, SE, SG, SI, SK, TJ, TM, TN, UA, VN, YU, ZA, ZW
only): **MARX, Degenhard**; Obere Reute 15, 78345 Moos
(DE).

(72) Inventors (for AE, AL, AM, AT, AU, AZ, BA, BE, BG, BR,
BY, CH, CN, CO, CY, CZ, DE, DK, DZ, EC, EE, ES, FI, FR,
GB, GE, GR, HR, HU, ID, IE, IL, IN, IS, IT, JP, KG,
KR, KZ, LT, LU, LV, MA, MC, MD, MK, MX, NL, NO, NZ,

PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TN, TR, UA, VN,
YU, ZA, ZW only): **KLEY, Hans-Peter**; Im Weinberg 3b,
78476 Allensbach (DE). **CHRISTIAANS, Johannes A.**
M.; Zevenwouden 233, NL-3524 CR UTRECHT (NL).

(72) Inventor (for AE, AL, AM, AT, AU, AZ, BA, BE, BG, BR,
BY, CH, CN, CO, CY, CZ, DE, DK, DZ, EC, EE, ES, FI,
FR, GB, GE, GR, HR, HU, ID, IE, IL, IN, IS, IT, JP, KG,
KR, KZ, LT, LU, LV, MA, MC, MD, MK, MX, NL, NO, PL,
PT, RO, RU, SE, SG, SI, SK, TJ, TM, TN, TR, UA, VN, YU,
ZA, ZW only): **MENGE, Wiro, M.P.B.**; Pontanuslaan 11,
NL-6821 HM ARNHEM (NL).

(72) Inventor; and
(75) Inventor/Applicant (for US only): **STERK, Geert, Jan**
[NL/NL]; Stadhouderslaan 38, NL-3583 JJ UTRECHT
(NL).

(74) Agent: **WILD, Robert**; c/o ALTANA Pharma AG, Byk-
Gulden-Strasse 2, 78467 Konstanz (DE).

(81) Designated States (national): AE, AL, AU, BA, BR, CA,
CN, CO, DZ, EC, GE, HR, ID, IL, IN, IS, JP, KR, LT, LV,
MA, MK, MX, NO, NZ, PH, PL, SG, TN, UA, US, VN,
YU, ZA, ZW.

(84) Designated States (regional): Eurasian patent (AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE,
BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU,
IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AL, AU, BA, BR, CA, CN, CO, DZ, EC, GE, HR, ID, IL, IN, IS, JP, KR, LT, LV, MA, MK, MX, NO, NZ, PH, PL, SG, TN, UA, VN, YU, ZA, ZW, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR)
- of inventorship (Rule 4.17(iv)) for US only

Published:

- with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PIPERIDINE-PYRIDAZONES AND PHTHALAZONES AS PDE4 INHIBITORS

(57) Abstract: The compounds of a certain formula 1, in which the given substituents have the meanings as indicated in the description, are novel effective PDE4 inhibitors.

WO 2004/017974 A1

PIPERIDINE-PYRIDAZONES AND PHTHALAZONES AS PDE4 INHIBITORS

Field of application of the invention

The invention relates to novel piperidine-derivatives, which are used in the pharmaceutical industry for the production of pharmaceutical compositions.

Known technical background

International Patent Applications WO98/31674 (= USP 6,103,718), WO99/31071, WO99/31090, WO99/47505 (= USP 6,255,303), WO01/19818, WO01/30766, WO01/30777, WO01/94319, WO02/064584, WO02/085885 and WO02/085906 disclose phthalazinone derivatives having PDE4 inhibitory properties. In the International Patent Application WO94/12461 and in the European Patent Application EP 0 763 534 3-aryl-pyridazin-6-one and arylalkyl-diazinone derivatives are described as selective PDE4 inhibitors. International Patent Application WO93/07146 (= USP 5,716,954) discloses benzo and pyrido pyridazinone and pyridazinthione compounds with PDE4 inhibiting activity.

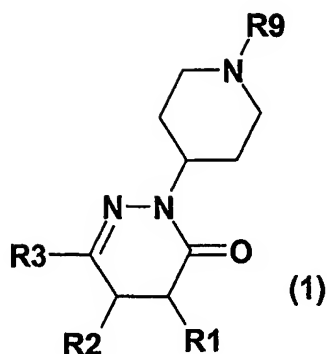
In the Journal of Medicinal Chemistry, Vol. 33, No. 6, 1990, pp. 1735-1741 1,4-Bis(3-oxo-2,3-dihydropyridazin-6-yl)benzene derivatives are described as potent phosphodiesterase inhibitors and inodilators. In the Journal of Medicinal Chemistry Vol. 45 No.12, 2002, pp. 2520-2525, 2526-2533 and in Vol. 44, No. 16, 2001, pp. 2511-2522 and pp. 2523-2535 phthalazinone derivatives are described as selective PDE4 inhibitors.

Description of the invention

It has now been found that the piperidine-derivatives, which are described in greater details below, have surprising and particularly advantageous properties.

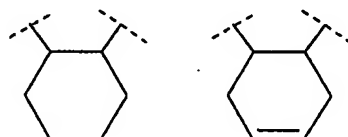
In a first aspect the invention relates to compounds of formula 1

- 2 -

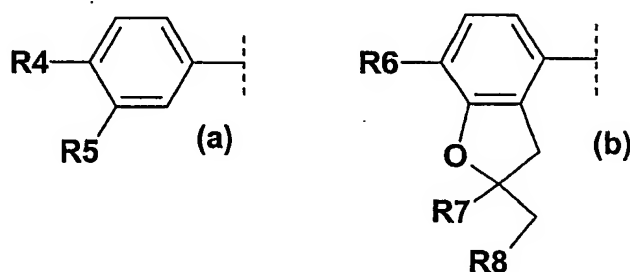


in which

R1 and R2 represent independently from one another hydrogen or 1-4C-alkyl, or R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is 1-4C-alkyl and

R8 is hydrogen or 1-4C-alkyl,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is Aryl1, Aryl2 substituted by R10 and R11, $-(CH_2)_n-C(O)-R12$, $-C(O)-(CH_2)_m-R13$, $-(CH_2)_p-R14$ or $-Y-(CH_2)_q-Z-(CH_2)_r-R16$,

wherein

Aryl1 is naphthyl, pyrazinyl, pyridazinyl, pyrimidin-4-yl, pyrimidin-5-yl, quinazolinyl, quinoxaliny, cinnoliny, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl or thiophenyl,

Aryl2 is naphthyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinazolinyl, quinoxaliny, cinnoliny, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R10 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylamino-carbonyl,

R11 is hydrogen, halogen, amino, nitro, 1-4C-alkyl or 1-4C-alkoxy,

R12 is 4H-benzo[1,4]oxazin-3-one-6-yl, Aryl2 or Aryl2 substituted by R10 and R11,

R13 is 1-4C-alkoxy, phenoxy, naphthalenoxy or 2-oxo-1,2-dihydro-quinolin-6-yloxy,

R14 is Aryl 3, Aryl2 substituted by R10 and R11, phenyl substituted by R15,

wherein

Aryl3 is naphthyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinazolinyl, quinoxaliny, cinnoliny, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R15 is purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R16 is hydrogen, hydroxyl, 1-4C-alkoxy, hydroxy-2-4C-alkoxy, 1-4C-alkoxy-2-4C-alkoxy, mono- or di-1-4C-dialkylamino, 1-4C-alkoxycarbonyl, amino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino or -N(H)-C(O)-N(R18)R19,

Y represents a bond or -C(O)-,

Z represents a bond, -O-, -C(O)-, -C(O)-N(H)-, -N(H)-C(O)-, -N(R17)-, -S- or -S(O)₂-,

R17 is hydrogen or 1-4C-alkyl,

R18 and R19 are independent from each other hydrogen or 1-4C-alkyl, or R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-, 1-pyrrolidinyl-, 1-piperidinyl-, 1-hexahydroazepino- or a 1-piperazinyl-ring,

n is an integer from 1 to 4,

m is an integer from 1 to 4,

p is an integer from 1 to 4,

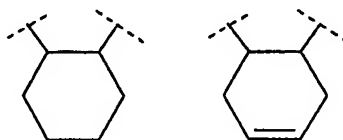
q is an integer from 1 to 4,

r is an integer from 1 to 4,

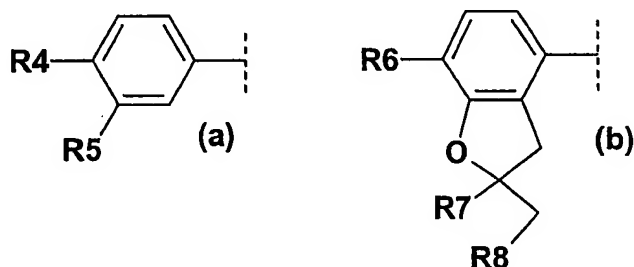
and the salts of these compounds – with the proviso that all those compounds of formula 1 are excluded in which Y and Z both represent a bond and simultaneously R16 is hydrogen, aminocarbonyl or mono- or di-1-4C-alkyl-aminocarbonyl, or in which Y represents -C(O)-, Z represents a bond and simul-

taneously R16 is hydrogen, amino or mono- or di-1-4C-alkylamino - for use in the treatment of diseases.

In a second aspect the invention relates to the use of compounds of formula 1 in which R1 and R2 represent independently from one another hydrogen or 1-4C-alkyl, or R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is 1-4C-alkyl and

R8 is hydrogen or 1-4C-alkyl,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is Aryl1, Aryl2 substituted by R10 and R11, $-(CH_2)_n-C(O)-R12$, $-C(O)-(CH_2)_m-R13$, $-(CH_2)_p-R14$ or $-Y-(CH_2)_q-Z-(CH_2)_r-R16$,

wherein

Aryl1 is naphthyl, pyrazinyl, pyridazinyl, pyrimidin-4-yl, pyrimidin-5-yl, quinazolinyl, quinoxalinyl, cinnolinyl, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl or thiophenyl,

Aryl2 is naphthyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinazolinyl, quinoxalinyl, cinnolyl, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R10 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylamino-carbonyl,

R11 is hydrogen, halogen, amino, nitro, 1-4C-alkyl or 1-4C-alkoxy,

R12 is 4H-benzo[1,4]oxazin-3-one-6-yl, Aryl2 or Aryl2 substituted by R10 and R11,

R13 is 1-4C-alkoxy, phenoxy, naphthalenoxy or 2-oxo-1,2-dihydro-quinolin-6-yloxy,

R14 is Aryl 3, Aryl2 substituted by R10 and R11, phenyl substituted by R15,

wherein

Aryl3 is naphthyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinazolinyl, quinoxalinyl, cinnolyl, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R15 is purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R16 is hydrogen, hydroxyl, 1-4C-alkoxy, hydroxy-2-4C-alkoxy, 1-4C-alkoxy-2-4C-alkoxy, mono- or di-1-4C-dialkylamino, 1-4C-alkoxycarbonyl, amino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino or -N(H)-C(O)-N(R18)R19,

Y represents a bond or -C(O)-,

Z represents a bond, -O-, -C(O)-, -C(O)-N(H)-, -N(H)-C(O)-, -N(R17)-, -S- or -S(O)₂,

R17 is hydrogen or 1-4C-alkyl,

R18 and R19 are independent from each other hydrogen or 1-4C-alkyl, or R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-, 1-pyrrolidinyl-, 1-piperidinyl-, 1-hexahydroazepino- or a 1-piperazinyl-ring,

n is an integer from 1 to 4,

m is an integer from 1 to 4,

p is an integer from 1 to 4,

q is an integer from 1 to 4,

r is an integer from 1 to 4,

and the salts of these compounds – with the proviso that all those compounds of formula 1 are excluded in which Y and Z both represent a bond and simultaneously R16 is hydrogen, aminocarbonyl or mono- or di-1-4C-alkylaminocarbonyl, or in which Y represents -C(O)-, Z represents a bond and simultaneously R16 is hydrogen, amino or mono- or di-1-4C-alkylamino - for the preparation of pharmaceutical compositions for the treatment of diseases which can be ameliorated by the administration of PDE4 inhibitors.

1-4C-Alkyl is a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and methyl radicals.

1-4C-Alkoxy is a radical which, in addition to the oxygen atom, contains a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Alkoxy radicals having 1 to 4 carbon atoms which may be mentioned in this context are, for example, the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy, ethoxy and methoxy radicals.

1-8C-Alkoxy is a radical which, in addition to the oxygen atom, contains a straight-chain or branched alkyl radical having 1 to 8 carbon atoms. Alkoxy radicals having 1 to 8 carbon atoms which may be mentioned in this context are, for example, the octyloxy, heptyloxy, isoheptyloxy (5-methylhexyloxy), hexyloxy, isohexyloxy (4-methylpentyloxy), neoheptyloxy (3,3-dimethylbutoxy), pentyloxy, isopentyloxy (3-methylbutoxy), neopentyloxy (2,2-dimethylpropoxy), butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy, ethoxy and methoxy radicals.

3-7C-Cycloalkoxy stands for cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy or cycloheptyloxy, of which cyclopropyloxy, cyclobutyloxy and cyclopentyloxy are preferred.

3-7C-Cycloalkylmethoxy stands for cyclopropylmethoxy, cyclobutylmethoxy, cyclopentylmethoxy, cyclohexylmethoxy or cycloheptylmethoxy, of which cyclopropylmethoxy, cyclobutylmethoxy and cyclopentylmethoxy are preferred.

3-5C-Cycloalkoxy stands for cyclopropyloxy, cyclobutyloxy and cyclopentyloxy.

3-5C-Cycloalkylmethoxy stands for cyclopropylmethoxy, cyclobutylmethoxy and cyclopentylmethoxy.

1-4C-Alkoxy which is completely or predominantly substituted by fluorine is, for example, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,2,2-trifluoroethoxy and in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and the difluoromethoxy radical, of which the difluoromethoxy radical is preferred. "Predominantly" in this connection means that more than half of the hydrogen atoms of the 1-4C-alkoxy group are replaced by fluorine atoms.

As spiro-linked 5-, 6- or 7-membered hydrocarbon rings, optionally interrupted by an oxygen or sulphur atom, may be mentioned the cyclopentane, cyclohexane, cycloheptane, tetrahydrofuran, tetrahydropyran and the tetrahydrothiophen ring.

1-4C-Alkoxy carbonyl is a carbonyl group to which one of the abovementioned 1-4C-alkoxy radicals is bonded. Examples which may be mentioned are the methoxycarbonyl [$\text{CH}_3\text{O}-\text{C}(\text{O})-$] and the ethoxycarbonyl [$\text{CH}_3\text{CH}_2\text{O}-\text{C}(\text{O})-$] radical.

Hydroxy-2-4C-alkoxy stands for one of the abovementioned 2-4C-alkoxy radicals, which is substituted by hydroxyl. An example is the 2-hydroxyethoxy radical $[-O-CH_2-CH_2-OH]$.

1-4C-Alkoxy-2-4C-alkoxy stands for a 2-4C-alkoxy radical which is substituted one of the abovementioned 1-4C-alkoxy radicals. Examples which may be mentioned are the 2-(methoxy)ethoxy $[-O-CH_2-CH_2-O-CH_3]$ and the 2-(ethoxy)ethoxy radical $[-O-CH_2-CH_2-O-CH_2-CH_3]$.

1-4C-Alkylcarbonyl is a carbonyl group to which one of the abovementioned 1-4C-alkyl radicals is bonded. An example is the acetyl radical $[CH_3C(O)-]$.

An 1-4C-Alkylcarbonylamino radical is, for example, the propionylamino $[C_3H_7C(O)NH-]$ and the acetyl-amino radical $[CH_3C(O)NH-]$.

Mono- or Di-1-4C-alkylamino radicals contain in addition to the nitrogen atom, one or two of the abovementioned 1-4C-alkyl radicals. Preferred are the di-1-4C-alkylamino radicals, especially the dimethylamino, the diethylamino and the diisopropylamino radical.

Mono- or Di-1-4C-alkylaminocarbonyl radicals contain in addition to the carbonyl group one of the abovementioned mono- or di-1-4C-alkylamino radicals. Examples which may be mentioned are the N-methyl-, the N,N-dimethyl-, the N-ethyl-, the N-propyl-, the N,N-diethyl- and the N-isopropylaminocarbonyl radical.

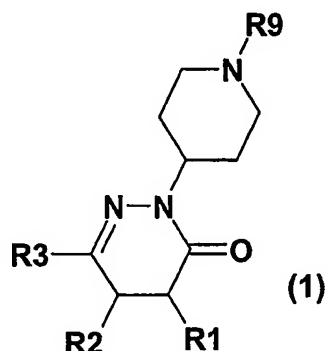
Suitable salts for compounds of the formula 1 are all acid addition salts. Particular mention may be made of the pharmacologically tolerable inorganic and organic acids customarily used in pharmacy. Those suitable are water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulphuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulphosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulphonic acid, methanesulphonic acid or 3-hydroxy-2-naphthoic acid, the acids being employed in salt preparation - depending on whether a mono- or polybasic acid is concerned and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

Pharmacologically intolerable salts, which can be obtained, for example, as process products during the preparation of the compounds according to the invention on an industrial scale, are converted into pharmacologically tolerable salts by processes known to the person skilled in the art.

According to expert's knowledge the compounds of the invention as well as their salts may contain, e.g. when isolated in crystalline form, varying amounts of solvents. Included within the scope of the inven-

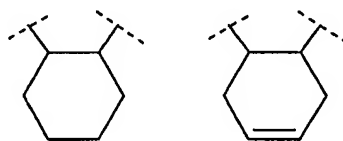
tion are therefore all solvates and in particular all hydrates of the compounds of formula 1 as well as all solvates and in particular all hydrates of the salts of the compounds of formula 1.

In a further aspect the invention relates to compounds of formula 1

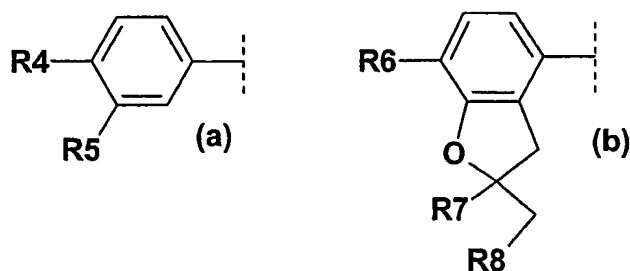


in which

R1 and R2 represent independently from one another hydrogen or 1-4C-alkyl, or R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is 1-4C-alkyl and

R8 is hydrogen or 1-4C-alkyl,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is Aryl1, Aryl2 substituted by R10 and R11, $-(CH_2)_n-C(O)-R12$, $-C(O)-(CH_2)_m-R13$, $-(CH_2)_p-R14$ or $-Y-(CH_2)_q-Z-(CH_2)_r-R16$,

wherein

Aryl1 is naphthyl, pyrazinyl, pyridazinyl, pyrimidin-4-yl, pyrimidin-5-yl, quinazolinyl, quinoxalinyl, cinnolinyl, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridiny, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl or thiophenyl,

Aryl2 is naphthyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinazolinyl, quinoxalinyl, cinnolinyl, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridiny, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R10 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylamino-carbonyl,

R11 is hydrogen, halogen, amino, nitro, 1-4C-alkyl or 1-4C-alkoxy,

R12 is 4H-benzo[1,4]oxazin-3-one-6-yl, Aryl2 or Aryl2 substituted by R10 and R11,

R13 is 1-4C-alkoxy, phenoxy, naphthalenoxy or 2-oxo-1,2-dihydro-quinolin-6-yloxy,

R14 is Aryl 3, Aryl2 substituted by R10 and R11, phenyl substituted by R15,

wherein

Aryl3 is naphthyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinazolinyl, quinoxalinyl, cinnolinyl, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridiny, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R15 is purinyl, pteridiny, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R16 is hydrogen, hydroxyl, 1-4C-alkoxy, hydroxy-2-4C-alkoxy, 1-4C-alkoxy-2-4C-alkoxy, mono- or di-1-4C-dialkylamino, 1-4C-alkoxycarbonyl, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino or $-N(H)-C(O)-N(R18)R19$,

Y represents a bond or $-C(O)-$,

Z represents a bond, $-O-$, $-C(O)-$, $-C(O)-N(H)-$, $-N(H)-C(O)-$, $-N(R17)-$, $-S-$ or $-S(O)_2-$,

R17 is hydrogen or 1-4C-alkyl,

R18 and R19 are independent from each other hydrogen or 1-4C-alkyl, or R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-, 1-pyrrolidinyl-, 1-piperidinyl-, 1-hexahydroazepino- or a 1-piperazinyl-ring,

n is an integer from 1 to 4,

m is an integer from 1 to 4,

p is an integer from 1 to 4,

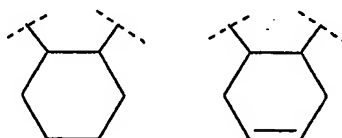
q is an integer from 1 to 4,

r is an integer from 1 to 4,

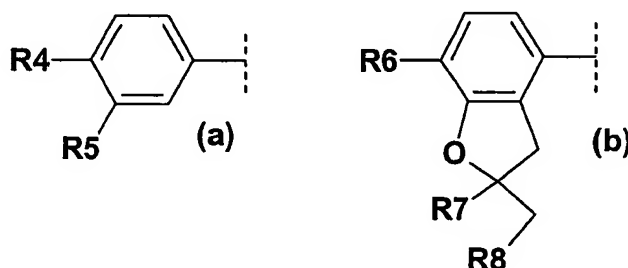
and the salts of these compounds – with the proviso that all those compounds of formula 1 are excluded in which Y and Z both represent a bond and simultaneously R16 is hydrogen, aminocarbonyl or mono- or di-1-4C-alkyl-aminocarbonyl, or in which Y represents $-C(O)-$, Z represents a bond and simultaneously R16 is hydrogen or mono- or di-1-4C-alkylamino.

Compound of formula 1 to be emphasized are those in which

R1 and R2 represent independently from one another hydrogen or 1-4C-alkyl, or R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-4C-alkoxy,

R6 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is methyl and

R8 is hydrogen,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane, cyclohexane, tetrahydrofurane or tetrahydropyran ring,

R9 is Aryl1, Aryl2 substituted by R10 and R11, $-(CH_2)_n-C(O)-R12$, $-C(O)-(CH_2)_m-R13$, $-(CH_2)_p-R14$ or $-Y-(CH_2)_q-Z-(CH_2)_r-R16$,

wherein

Aryl1 is pyrimidin-4-yl, pyrimidin-5-yl, quinazolinyl, quinolyl, isoquinolyl, indolyl, indazolyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl or thiophenyl,

Aryl2 is pyridyl, pyrimidinyl, quinazolinyl, quinolyl, isoquinolyl, indolyl, indazolyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R10 is halogen, nitro, cyano, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylaminocarbonyl,

R11 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

R12 is 4H-benzo[1,4]oxazin-3-one-6-yl, Aryl2 or Aryl2 substituted by R10 and R11,

R13 is phenoxy, naphthalenoxy or 2-oxo-1,2-dihydro-quinolin-6-yloxy,

R14 is Aryl 3, Aryl2 substituted by R10 and R11, phenyl substituted by R15,

wherein

Aryl3 is pyrimidinyl, quinazolinyl, quinolyl, isoquinolyl, indolyl, indazolyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R15 is purinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, furanyl or thiophenyl,

Y represents a bond or $-C(O)-$,

Z represents a bond, $-O-$, $-S-$ or $-S(O)_2-$,

R16 is hydrogen, hydroxyl, 1-4C-alkoxy, hydroxy-2-4C-alkoxy, 1-4C-alkoxy-2-4C-alkoxy or $-N(H)-C(O)-N(R18)R19$,

wherein

R18 and R19 are independent from each other hydrogen or 1-4C-alkyl, or R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-, 1-pyrrolidinyl- or 1-piperidinyl -ring,

n is an integer from 1 to 2,

m is an integer from 1 to 3,

p is an integer from 1 to 2,

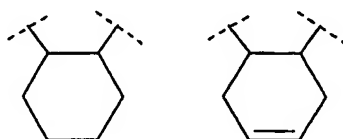
q is an integer from 1 to 3,

r is an integer from 1 to 2,

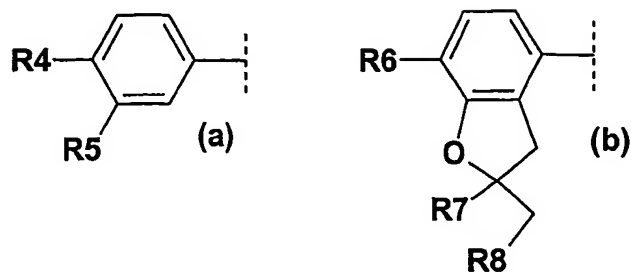
and the salts of these compounds – with the proviso that all those compounds of formula 1 are excluded in which Y and Z both represent a bond and simultaneously R16 is hydrogen, or in which Y represents $-C(O)-$, Z represents a bond and simultaneously R16 is hydrogen.

Preferred compounds of formula 1 are those, in which

R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a benzene derivative of formulae (a) or (b)



wherein

R4 is 1-2C-alkoxy,

R5 is 1-4C-alkoxy,

R6 is 1-2C-alkoxy,

R7 is methyl and

R8 is hydrogen,

R9 is $-(CH_2)_n-C(O)-R_{12}$, $-C(O)-(CH_2)_m-R_{13}$, $-(CH_2)_p-R_{14}$ or $-Y-(CH_2)_q-Z-(CH_2)_r-R_{16}$,

wherein

R12 is benzofuran-2-yl or 4H-benzo[1,4]oxazin-3-one-6-yl,

R13 is 2-oxo-1,2-dihydro-quinolin-6-yloxy,

R14 is phenyl substituted by R15,

wherein

R15 is benzimidazolyl,

Y represents a bond or $-C(O)-$,

Z represents a bond, $-O-$, $-S-$ or $-S(O)_2-$,

R16 is hydrogen, hydroxyl, methoxy, hydroxyethoxy, methoxyethoxy or $-N(H)-C(O)-N(R_{18})R_{19}$,

wherein

R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-ring,

n is 1,

m is an integer from 1 to 3,

p is 1,

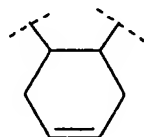
q is an integer from 1 to 2,

r is an integer from 1 to 2,

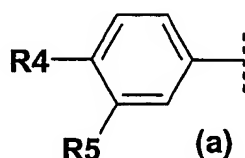
and the salts of these compounds – with the proviso that all those compounds of formula 1 are excluded in which Y and Z both represent a bond and simultaneously R16 is hydrogen, or in which Y represents $-C(O)-$, Z represents a bond and simultaneously R16 is hydrogen.

Particularly preferred compounds of formula 1 are those in which

R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form the following group



R3 represents a phenyl derivative of formula (a)



wherein

R4 is methoxy,

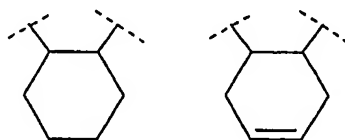
R5 is methoxy,

R9 is 2-(methanesulfonyl)ethanoyl, 2-benzofuran-2-yl-2-oxo-ethyl, 4-benzimidazol-1-ylbenzyl, 2-(4H-benzo[1,4]oxazin-3-one-6-yl)ethanoyl, 3-{2-[(1-morpholin-4-yl-methanoyl)-amino]-ethanesulfonyl}-propionyl, 2-(2-oxo-1,2-dihydroquinolin-6-yl)oxyethanoyl, 4-(2-oxo-1,2-dihydroquinolin-6-yl)oxybutanoyl, 2-methoxyethyl, 2-methylsulfanylethyl, 2-methanesulfonylethyl or 2-(2-hydroxyethoxy)ethyl,

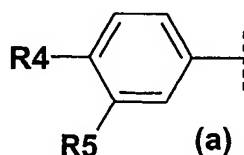
and the salts of these compounds.

An embodiment (embodiment A) of the compounds of formula 1 are those in which

R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a benzene derivative of formula (a)

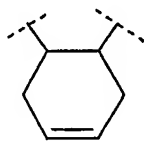


wherein

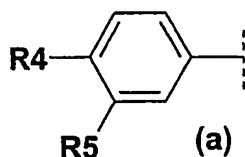
R4 is 1-2C-alkoxy,

R5 is 1-2C-alkoxy,
 R9 is $-(CH_2)_n-C(O)-R_{12}$, $-C(O)-(CH_2)_m-R_{13}$ or $-(CH_2)_p-R_{14}$,
 wherein
 R12 is benzofuran-2-yl or 4H-benzo[1,4]oxazin-3-one-6-yl,
 R13 is 2-oxo-1,2-dihydro-quinolin-6-yloxy,
 R14 is phenyl substituted by R15,
 wherein
 R15 is benzimidazolyl,
 n is 1,
 m is an integer from 1 to 3,
 p is 1,
 and the salts of these compounds.

Preferred compounds of formula 1 of embodiment A are those in which
 R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form the
 following group



R3 represents a phenyl derivative of formula (a)

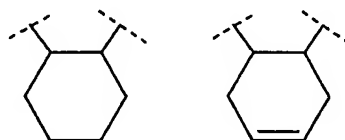


wherein

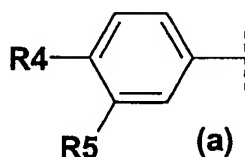
R4 is methoxy,
 R5 is methoxy,
 R9 is $-(CH_2)_n-C(O)-R_{12}$, $-C(O)-(CH_2)_m-R_{13}$ or $-(CH_2)_p-R_{14}$,
 wherein
 R12 is benzofuran-2-yl or 4H-benzo[1,4]oxazin-3-one-6-yl,
 R13 is 2-oxo-1,2-dihydro-quinolin-6-yloxy,
 R14 is phenyl substituted by R15,
 wherein
 R15 is benzimidazolyl,
 n is 1,
 m is an integer from 1 to 3,
 p is 1,

and the salts of these compounds.

Another embodiment (embodiment B) of the compounds of formula 1 are those in which R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a benzene derivative of formula (a)



wherein

R4 is 1-2C-alkoxy,

R5 is 1-2C-alkoxy,

R9 is $-Y-(CH_2)_q-Z-(CH_2)_r-R16$,

wherein

Y represents a bond or $-C(O)-$,

Z represents a bond, $-O-$, $-S-$ or $-S(O)_2-$,

R16 is hydrogen, hydroxyl or $-N(H)-C(O)-N(R18)R19$,

wherein

R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-ring,

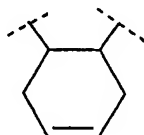
q is an integer from 1 to 2,

r is an integer from 1 to 2,

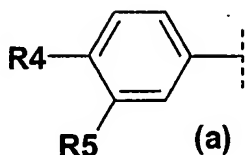
and the salts of these compounds – with the proviso that all those compounds of formula 1 are excluded in which Y and Z both represent a bond and simultaneously R16 is hydrogen, or in which Y represents $-C(O)-$, Z represents a bond and simultaneously R16 is hydrogen.

Preferred compounds of formula 1 of embodiment B are those in which

R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form the following group



R3 represents a phenyl derivative of formula (a)



wherein

R4 is methoxy,

R5 is methoxy,

R9 is $-Y-(CH_2)_q-Z-(CH_2)_r-R16$,

wherein

Y represents a bond or $-C(O)-$,

Z represents a bond, $-O-$, $-S-$ or $-S(O)_2-$,

R16 is hydrogen, hydroxyl or $-N(H)-C(O)-N(R18)R19$,

wherein

R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-ring,

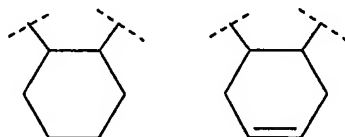
q is an integer from 1 to 2,

r is an integer from 1 to 2,

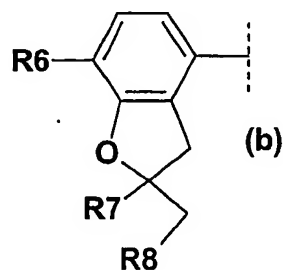
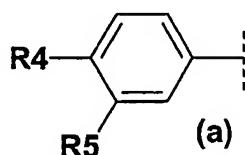
and the salts of these compounds – with the proviso that all those compounds of formula 1 are excluded in which Y and Z both represent a bond and simultaneously R16 is hydrogen, or in which Y represents $-C(O)-$, Z represents a bond and simultaneously R16 is hydrogen.

Further compounds of formula 1 (embodiment C) are those in which

R1 and R2 represent independently from one another hydrogen or 1-4C-alkyl, or R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is 1-4C-alkyl and

R8 is hydrogen or 1-4C-alkyl,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is Aryl1, Aryl2 substituted by R10 and R11, $-(CH_2)_n-C(O)-R12$, $-C(O)-(CH_2)_m-R13$, $-(CH_2)_p-R14$ or $-Y-(CH_2)_q-Z-(CH_2)_r-R16$,

wherein

Aryl1 is naphthyl, pyrazinyl, pyridazinyl, pyrimidin-4-yl, pyrimidin-5-yl, quinazolinyl, quinoxalinyl, cinnolyl, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl or thiophenyl,

Aryl2 is naphthyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinazolinyl, quinoxalinyl, cinnolyl, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R10 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylamino-carbonyl,

R11 is hydrogen, halogen, amino, nitro, 1-4C-alkyl or 1-4C-alkoxy,

R12 is 4H-benzo[1,4]oxazin-3-one-6-yl, Aryl2 or Aryl2 substituted by R10 and R11,

R13 is 1-4C-alkoxy, phenoxy, naphthalenoxy or 2-oxo-1,2-dihydro-quinolin-6-yloxy,

R14 is Aryl 3, Aryl2 substituted by R10 and R11, phenyl substituted by R15,

wherein

Aryl3 is naphthyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinazolinyl, quinoxalinyl, cinnolyl, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R15 is purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R16 is hydrogen, hydroxyl, 1-4C-alkoxy, hydroxy-2-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, mono- or di-1-4C-dialkylamino, 1-4C-alkoxycarbonyl, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino or $-N(H)-C(O)-N(R18)R19$,

Y represents a bond or $-C(O)-$,

Z represents a bond, $-O-$, $-C(O)-$, $-C(O)-N(H)-$, $-N(H)-C(O)-$, $-N(R17)-$, $-S-$ or $-S(O)_2-$,

R17 is hydrogen or 1-4C-alkyl,

R18 and R19 are independent from each other hydrogen or 1-4C-alkyl, or R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-, 1-pyrrolidinyl-, 1-piperidinyl-, 1-hexahydroazepino- or a 1-piperazinyl-ring,

n is an integer from 1 to 4,

m is an integer from 1 to 4,

p is an integer from 1 to 4,

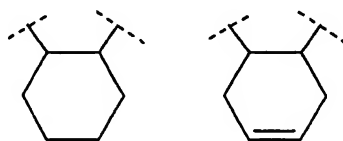
q is an integer from 1 to 4,

r is an integer from 1 to 4,

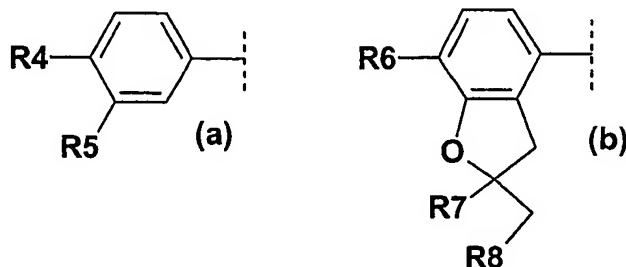
and the salts of these compounds – with the proviso that all those compounds of formula 1 are excluded in which Y and Z both represent a bond and R16 is hydrogen.

Compounds of formula 1 of embodiment C to be emphasized are those in which

R1 and R2 represent independently from one another hydrogen or 1-4C-alkyl, or R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-4C-alkoxy,

R6 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is methyl and

R8 is hydrogen,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane, cyclohexane, tetrahydrofurane or tetrahydropyran ring,

R9 is Aryl1, Aryl2 substituted by R10 and R11, $-(CH_2)_n-C(O)-R12$, $-C(O)-(CH_2)_m-R13$, $-(CH_2)_p-R14$ or $-Y-(CH_2)_q-Z-(CH_2)_r-R16$,

wherein

Aryl1 is pyrimidin-4-yl, pyrimidin-5-yl, quinazolinyl, quinolyl, isoquinolyl, indolyl, indazolyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl or thiophenyl,

Aryl2 is pyridyl, pyrimidinyl, quinazolinyl, quinolyl, isoquinolyl, indolyl, indazolyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R10 is halogen, nitro, cyano, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylaminocarbonyl,

R11 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

R12 is 4H-benzo[1,4]oxazin-3-one-6-yl, Aryl2 or Aryl2 substituted by R10 and R11,

R13 is phenoxy, naphthalenoxy or 2-oxo-1,2-dihydro-quinolin-6-yloxy,

R14 is Aryl 3, Aryl2 substituted by R10 and R11, phenyl substituted by R15,

wherein

Aryl3 is pyrimidinyl, quinazolinyl, quinolyl, isoquinolyl, indolyl, indazolyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R15 is purinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, furanyl or thiophenyl,

Y represents a bond or $-C(O)-$,

Z represents a bond, $-O-$, $-S-$ or $-S(O)_2-$,

R16 is hydrogen, hydroxyl, 1-4C-alkoxy, hydroxy-2-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy or $-N(H)-C(O)-N(R18)R19$,

wherein

R18 and R19 are independent from each other hydrogen or 1-4C-alkyl, or R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-, 1-pyrrolidinyl- or 1-piperidinyl -ring,

n is an integer from 1 to 2,

m is an integer from 1 to 3,

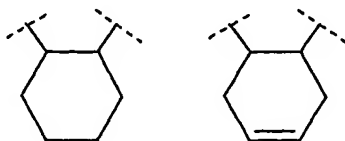
p is an integer from 1 to 2,

q is an integer from 1 to 3,

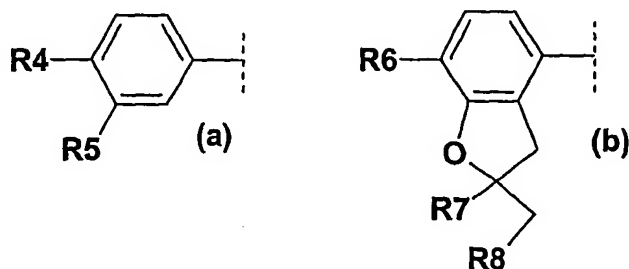
r is an integer from 1 to 2,

and the salts of these compounds – with the proviso that all those compounds of formula 1 are excluded in which Y and Z both represent a bond and R16 is hydrogen.

Compounds of formula 1 of embodiment C particularly to be emphasized are those in which R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a benzene derivative of formulae (a) or (b)



wherein

R4 is 1-2C-alkoxy,

R5 is 1-4C-alkoxy,

R6 is 1-2C-alkoxy,

R7 is methyl and

R8 is hydrogen,

R9 is $-(CH_2)_n-C(O)-R_{12}$, $-C(O)-(CH_2)_m-R_{13}$, $-(CH_2)_p-R_{14}$ or $-Y-(CH_2)_q-Z-(CH_2)_r-R_{16}$,
wherein

R12 is benzofuran-2-yl or 4H-benzo[1,4]oxazin-3-one-6-yl,

R13 is 2-oxo-1,2-dihydro-quinolin-6-yloxy,

R14 is phenyl substituted by R15,

wherein

R15 is benzimidazolyl,

Y represents a bond or $-C(O)-$,

Z represents a bond, $-O-$, $-S-$ or $-S(O)_2-$,

R16 is hydrogen, hydroxyl, methoxy, hydroxyethoxy, methoxyethoxy or $-N(H)-C(O)-N(R_{18})R_{19}$,
wherein

R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded,
form a 4-morpholinyl-ring,

n is 1,

m is an integer from 1 to 3,

p is 1,

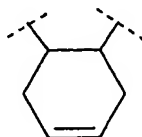
q is an integer from 1 to 3,

r is an integer from 1 to 2,

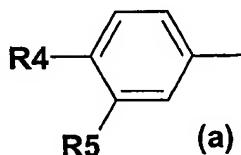
and the salts of these compounds – with the proviso that all those compounds of formula 1 are excluded in which Y and Z both represent a bond and R16 is hydrogen.

Preferred compounds of formula 1 of embodiment C are those in which

R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form the following group



R3 represents a phenyl derivative of formula (a)



wherein

R4 is methoxy,

R5 is methoxy,

R9 is 2-(methanesulfonyl)ethanoyl, 2-benzofuran-2-yl-2-oxo-ethyl, 4-benzimidazol-1-ylbenzyl, 2-(4H-benzo[1,4]oxazin-3-one-6-yl)ethanoyl, 2-(2-oxo-1,2-dihydroquinolin-6-yloxy)ethanoyl, 4-(2-oxo-1,2-dihydroquinolin-6-yloxy)butanoyl, 2-methoxyethyl, 2-methylsulfanylethyl, 2-methanesulfonylethyl or 2-(2-hydroxy-ethoxy)ethyl,

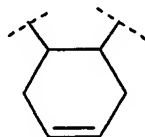
and the salts of these compounds.

A special embodiment of the compounds of the present invention include those compounds of formula 1 in which R3 represents a phenyl derivative of formula (a).

Another special embodiment of the compounds of the present invention include those compounds of formula 1 in which R3 represents a phenyl derivative of formula (a) and R4 and R5 have the meaning methoxy.

A further special embodiment of the compounds of the present invention include those compounds of formula 1 in which R1 and R2 are hydrogen, R3 represents a phenyl derivative of formula (a) and R4 and R5 have the meaning methoxy.

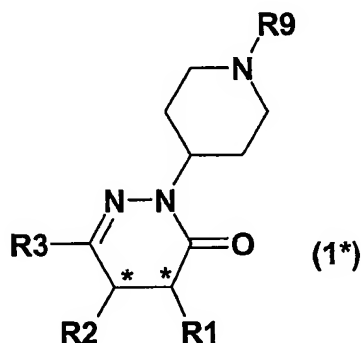
Still a further special embodiment of the compounds of the present invention include those compounds of formula 1 in which R1 and R2 together and with inclusion of the two carbon atoms to which they are bonded form the following group



R3 represents a phenyl derivative of formula (a) and R4 and R5 have the meaning methoxy.

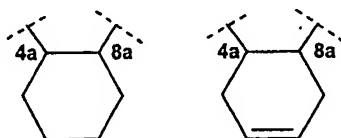
The compounds of formula 1 are chiral compounds with - depending on the meaning of R3 - a chiral center in the phenyl derivative of formula b, if the substituents -R7 and -CH₂R8 are not identical. However, preferred are those compounds, in which the substituents -R7 and -CH₂R8 are identical or together and with inclusion of the carbon atoms to which they are bonded form a spiro-connected 5-, 6- or 7-membered hydrocarbon ring.

Further possible chiral centers in the compounds of formula 1 are marked in the following formula 1* with an asterix (*):



The invention includes all conceivable pure diastereomers and pure enantiomers, as well as all mixtures thereof independent from the ratio, including the racemates.

In those cases, wherein R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



those compounds are preferred, in which the hydrogen atoms in the positions 4a and 8a are cis-configured. Especially preferred in this connection are those compounds, in which the absolute configuration (according to the rules of Cahn, Ingold and Prelog) is S in the position 4a and R in the position 8a.

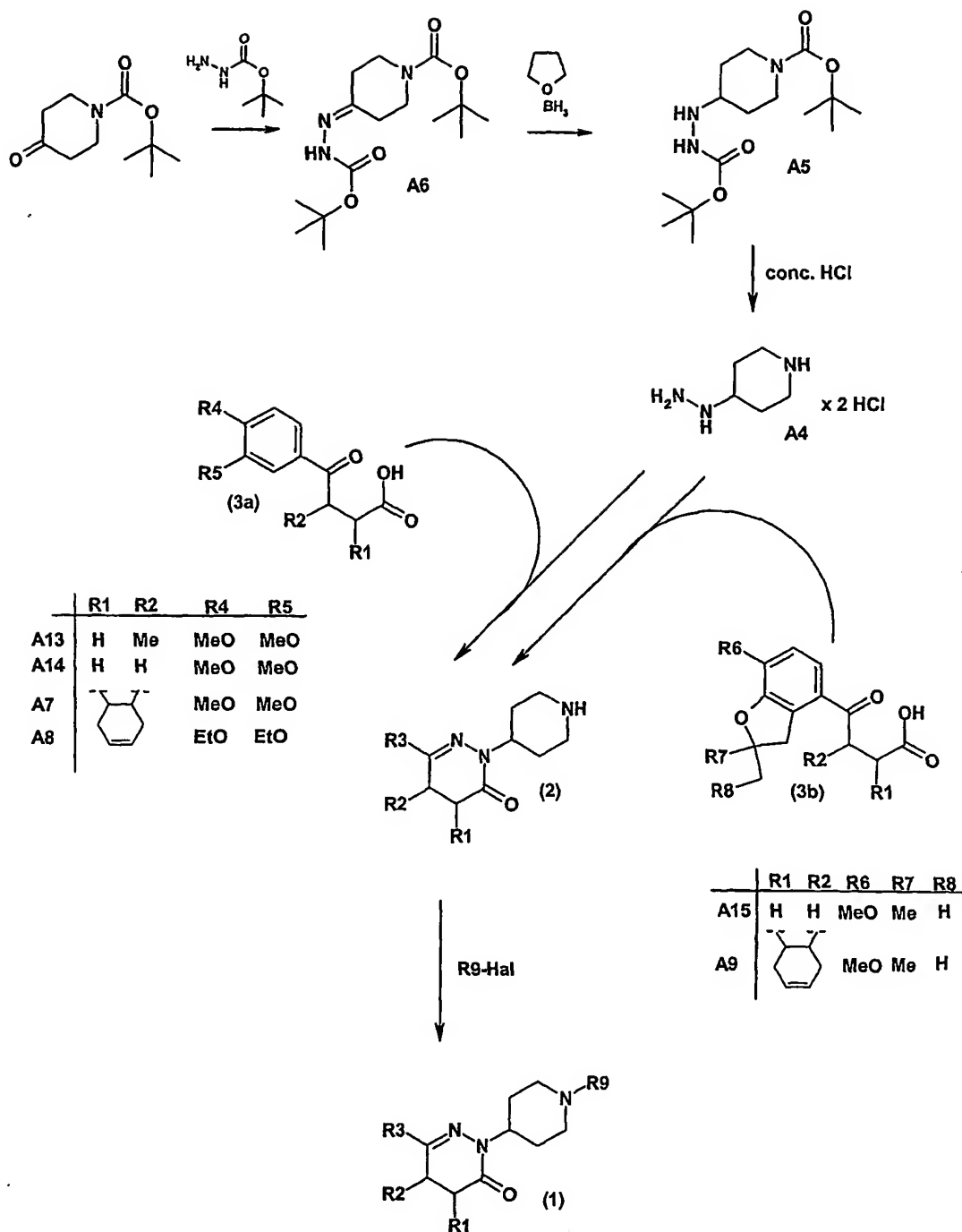
(4a,8a)-cis-Racemates can be split up into the corresponding enantiomers by methods known by a person skilled in the art. Preferably the racemic mixtures are separated into two diastereomers during the preparation with the help of an optical active separation agent on the stage of the cyclohexanecarboxylic acids or the 1,2,3,6-tetrahydrobenzoic acids (for example starting compounds A1 and A2). As separation agents may be mentioned, for example, optical active amines such as the (+)- and (-)-forms of 1-phenylethylamine [(R)-(+)-1-phenylethylamine = D- α -methylbenzylamine or (S)-(-)-1-phenylethylamine = L- α -methylbenzylamine) and ephedrine, the optical active alkaloids quinine, cinchonine, cinchonidine and brucine.

The preparation of (4aS, 8aR) configured 4-(3,4-dialkoxyphenyl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-ones or 4-(3,4-dialkoxyphenyl)-4a,5,6,7,8,8a-hexahydro-2H-phthalazin-1-ones is described, for example, in the international application WO98/31674.

The preparation of (4aS, 8aR) configured 4-(2,3-dihydro-7-alkoxybenzofuran-2-spiro-1'-cyclopentan-4-yl)-4a,5,6,7,8,8a-hexahydro-2H-phthalazin-1-ones is described, for example, in the international application WO99/31090.

The compounds according to the invention can be prepared, for example, as described in Reaction scheme 1.

Reaction scheme 1:



Reaction scheme 1 shows that the compounds of formula 1 can be, for example, prepared starting from 4-oxo-piperidine-1-carboxylic acid tert-butyl ester which is reacted in a first reaction step with tert-butylcarbrazate to give 4-(tert-Butoxycarbonyl-hydrazono)-piperidine-1-carboxylic acid tert-butyl ester (starting compound A6). Compound A6 is reduced with, for example, the boran tetrahydrofuran com-

plex to give 4-(N'-tert-Butoxycarbonyl-hydrazino)-piperidine-1-carboxylic acid tert-butyl ester (starting compound A5). Treatment of compound A5 with concentrated hydrochloric acid results in the formation of piperidin-4-yl-hydrazine dihydrochloride (starting compound A4).

The reaction of piperidin-4-yl-hydrazine dihydrochloride with phenyl-4-oxo-butyric acids, benzoyl-1,2,3,6-tetrahydrobenzoic acids or benzoyl-1,2,3,4,5,6-hexahydrobenzoic acids of formulae 3a or 3b leads to the piperidino derivatives of formula 2.

These are reacted in the final reaction step with compounds of formula R9-X, wherein X represents a suitable leaving group, preferably a chlorine atom, to give the compounds of formula 1.

For some compounds of formula 1, it can be advantageous, to introduce the substituent R9 in two reaction steps. As example may be mentioned those compounds of formula 1, wherein R9 represents $-Y-(CH_2)_q-Z-(CH_2)_r-R16$.

The preparation of phenyl-4-oxo-butyric acids, benzoyl-1,2,3,6-tetrahydrobenzoic acids or benzoyl-1,2,3,4,5,6-hexahydrobenzoic acids of formulae 3a or 3b is known to the person skilled in the art (see for example Starting compounds and Intermediates).

The preparation of compounds of formula R9-X is also known to the person skilled in the art.

Suitably, the conversions are carried out analogous to methods which are familiar per se to the person skilled in the art, for example, in the manner which is described in the following examples.

The substances according to the invention are isolated and purified in a manner known per se, e.g. by distilling off the solvent in vacuo and recrystallising the residue obtained from a suitable solvent or subjecting it to one of the customary purification methods, such as column chromatography on a suitable support material.

Salts are obtained by dissolving the free compound in a suitable solvent (for example a ketone like acetone, methylethylketone, or methylisobutylketone, an ether, like diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol, such as ethanol, isopropanol) which contains the desired acid, or to which the desired acid is then added. The salts are obtained by filtering, reprecipitating, precipitating with a non-solvent for the addition salt or by evaporating the solvent. Salts obtained can be converted by basification into the free compounds which, in turn, can be converted into salts. In this manner, pharmacologically non-tolerable salts can be converted into pharmacologically tolerable salts.

The following examples illustrate the invention in greater detail, without restricting it. As well, further compounds of formula 1, of which the preparation is explicitly not described, can be prepared in an

analogous way or in a way which is known by a person skilled in the art using customary preparation methods.

The compounds, which are mentioned in the examples as well as their salts are preferred compounds of the invention.

In the examples, RT stands for room temperature, h for hour(s), min for minute(s) and M. p. for melting point.

Examples

Final products

1. (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-[1-(2-methanesulfonyl-ethanoyl)-piperidin-4-yl]-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

A mixture of 10 mmol of starting compound A1, 12 mmol of methanesulfonyl-acetic acid and 10 mmol of triethylamine in 50 ml of dichloromethane is stirred for 60 min after which 20 mmol of (3-dimethylamino-propyl)-ethyl-carbodiimide hydrochloride is added. The resulting mixture is stirred for 18 h at RT and then successively washed with diluted hydrochloric acid and aqueous sodium carbonate. After drying over magnesium sulfate, the solvent is evaporated and the residue crystallised from methanol. M. p. 169-170°C

2. (4aS,8aR)-2-[1-(2-Benzofuran-2-yl-2-oxo-ethyl)-piperidin-4-yl]-4-(3,4-dimethoxy-phenyl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

A mixture of 5 mmol of starting compound A1, 6 mmol of 1-benzofuran-2-yl-2-chloro-ethanone and 20 mmol of potassium carbonate in 20 ml of dimethylformamide is stirred at RT. After 18 h 100 ml of water and 300 ml of diethyl ether is added to the mixture. The ether solution is dried over magnesium sulfate. On concentrating the solution, the title compound crystallised. M. p. 188-189°C

3. (4aS,8aR)-2-[1-(4-Benzimidazol-1-yl-benzyl)-piperidin-4-yl]-4-(3,4-dimethoxy-phenyl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one hydrochloride

A solution of 5 mmol of starting compound A1 in 100 ml of dichloromethane is washed with aqueous sodium carbonate and subsequently dried over magnesium sulfate and evaporated. The residue, together with 5 mmol of acetic acid and 5 mmol of 4-benzimidazol-1-yl-benzaldehyde is dissolved in 50 ml of methanol. The resulting mixture is stirred for 60 min after which 10 mmol of sodium cyanoborohydride is added. Stirring is continued at RT for another 18 h, after which the solvent is evaporated and the residue partitioned between water and ethyl acetate. The ethyl acetate solution is dried over magnesium sulfate and evaporated. The residue is purified by chromatography (elution with ethyl acetate). The pure fractions are collected and after addition of a saturated solution of hydrochloric acid in diethyl ether, the title compound precipitated. M. p. 147-149°C

4. 6-(2-[4-[(4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-1-oxo-4a,5,8,8a-tetrahydro-1H-phthalazin-2-yl]-piperidin-1-yl]-ethanoyl)-4H-benzo[1,4]oxazin-3-one

Prepared from starting compound A1 and 6-(2-chloro-ethanoyl)-4H-benzo[1,4]oxazin-3-one as described for compound 2. M. p. 209°C (with decomposition)

5. Morpholine-4-carboxylic acid [2-(3-{4-[4aS,8aR]-4-(3,4-dimethoxy-phenyl)-1-oxo-4a,5,8,8a-tetrahydro-1H-phthalazin-2-yl]-piperidin-1-yl}-3-oxo-propane-1-sulfonyl)-ethyl]-amide

A solution of 5 mmol of (4aS,8aR)-2-{1-[3-(2-amino-ethanesulfonyl)-propanoyl]-piperidin-4-yl}-4-(3,4-dimethoxy-phenyl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one (starting compound A18) and 20 mmol of triethylamine in 20 ml of dichloromethane is cooled to 0°C after which 7 mmol of morpholine-4-carbonyl chloride is added. The resulting mixture is stirred for 30 min after which it is washed with aqueous sodium carbonate. The dichloromethane solution is dried over magnesium sulfate and evaporated. The residue is crystallized from ethyl acetate. M. p. 118-121°C

6. (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-{1-[2-(2-oxo-1,2-dihydro-quinolin-6-yloxy)-ethanoyl]-piperidin-4-yl}-4a,5,8,8a-tetrahydro-2 H-phthalazin-1-one

Prepared from starting compounds A1 and A16 as described for compound 1. Crystallized from a mixture of ethyl acetate and hexane. M. p. 134 °C (with decomposition)

7. (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-{1-[4-(2-oxo-1,2-dihydro-quinolin-6-yloxy)-butanoyl]-piperidin-4-yl}-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

Prepared from starting compounds A1 and A17 as described for compound 1. Crystallized from a mixture of ethyl acetate and hexane. M. p. 146-149°C

8. (4aS,8aR)-2-{1-[2-(2-Amino-ethoxy)-ethyl]-piperidin-4-yl}-4-(3,4-dimethoxy-phenyl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one dihydrochloride

A mixture of 10 mmol of starting compound A1, 10 mmol of N-[2-(2-Bromo-ethoxy)-ethyl]-phthalimide and 20 mmol of potassium carbonate in 50 ml of dimethylformamide is stirred at RT. After about 18 h, the mixture is poured into water and this mixture is extracted with diethyl ether. The ether extract is dried over magnesium sulfate and evaporated. The residue is dissolved in ethanol and to this solution, 40 mmol of hydrazine hydrate is added. The resulting mixture is refluxed for 20 h and subsequently evaporated. The residue is partitioned between ethyl acetate and aqueous sodium carbonate. The organic layer is dried over magnesium sulfate and to this solution, a saturated solution of hydrochloric acid in diethyl ether is added. The precipitate is filtered off and dried. M. p. 86-89°C

9. (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-[1-(2-methoxy-ethyl)-piperidin-4-yl]-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one hydrochloride

A mixture of 10 mmol of starting compound A1, 13 mmol of 1-chloro-2-methoxy-ethane and 20 mmol of potassium carbonate in 50 ml of dimethylformamide is stirred at RT. After about 18 h, the mixture is poured into water and this mixture is extracted with diethyl ether. The ether extract is dried over magnesium sulfate and evaporated. The residue is purified by chromatography (elution with a mixture of ethyl acetate and methanol, 2:1). After evaporating the eluents, the residue is dissolved in ethanol. To this a solution, a saturated solution of hydrochloric acid in diethyl ether is added. The precipitate is filtered off and dried. M. p. 87-90°C

10. (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-[1-(2-methylsulfanyl-ethyl)-piperidin-4-yl]-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one hydrochloride

Prepared from starting compound A1 and 1-chloro-2-methylsulfanyl-ethane as described for compound 10. M. p. 210°C (with decomposition)

11. (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-[1-(2-methanesulfonyl-ethyl)-piperidin-4-yl]-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one hydrochloride

To a solution of 5 mmol of compound 11 in 100 ml of dichloromethane at 0°C, 11 mmol of 3-chloroperbenzoic acid is added. The resulting mixture is stirred for 1 h after which it is washed with aqueous sodium carbonate. The dichloromethane solution is dried over magnesium sulfate and evaporated. The residue is purified by chromatography (elution with a mixture of ethyl acetate and methanol, 2:1). To the pure fraction, a saturated solution of hydrochloric acid in diethyl ether is added. The precipitate is filtered off and dried. M. p. 87-90°C

12. (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-[1-[2-(2-hydroxy-ethoxy)-ethyl]-piperidin-4-yl]-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

Prepared from starting compound A1 and 2-(2-chloro-ethoxy)-ethanol as described for compound 10. Crystallized as the free base from ethyl acetate. M. p. 204-207°C

13. (4aS,8aR)-2-[1-[3-(2-Amino-ethylsulfanyl)-propanoyl]-piperidin-4-yl]-4-(3,4-dimethoxy-phenyl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

Prepared as described in WO01/94319.

14. (4a*S*,8a*R*)-2-{1-[3-(2-Amino-ethylsulfonyl)-propanoyl]-piperidin-4-yl}-4-(3,4-dimethoxy-phenyl)-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one hydrochloride

Prepared as described in WO01/94319.

15. 6-(4-{4-[3-(3,4-Dimethoxy-phenyl)-6-oxo-5,6-dihydro-4*H*-pyridazin-1-yl]-piperidin-1-yl}-4-oxo-butoxy)-1*H*-quinolin-2-one

1.00 g 6-(3,4-Dimethoxy-phenyl)-2-piperidin-4-yl-4,5-dihydro-2*H*-pyridazin-3-one hydrochloride, 1.43 g 4-(2-Oxo-1,2-dihydro-quinolin-6-yl-oxy)-butyric acid and 0.6 ml triethylamine are dissolved in 20 ml DMF and stirred. 1.00 g 1-[3-dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride is added and the mixture is stirred for 15 h. The solvent is evaporated and the residue dissolved in 100 ml dichloromethane and washed with dilute hydrochloric acid, dilute sodium hydroxide and water, dried, filtered and concentrated in vacuo. The crude product is crystallized from ethyl acetate/ethanol.

M. p. 169-171°C

Starting Compounds and Intermediates**A1. (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-piperidin-4-yl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one hydrochloride**

A solution of 50 mmol of the salt of (S)-(-)- α -methylbenzylamine and (cis)-2-(3,4-dimethoxybenzoyl)-1,2,3,6-tetrahydrobenzoic acid (starting compound A7), 55 mmol of piperidin-4-yl-hydrazine dihydrochloride and 100 mmol of triethylamine in 150 ml of 1-propanol is refluxed for 18 h. After cooling to RT, the precipitate is filtered off and dried. M. p. 285-288°C

A2. (4aS,8aR)-4-(3,4-Diethoxy-phenyl)-2-piperidin-4-yl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one hydrochloride

Prepared from the salt of (S)-(-)- α -methylbenzylamine and (cis)-2-(3,4-diethoxybenzoyl)-1,2,3,6-tetrahydrobenzoic acid (starting compound A8) in 2-propanol as described for compound A1. M. p. 248-250°C

A3. (cis)-4-(7-Methoxy-2,2-dimethyl-2,3-dihydro-benzofuran-4-yl)-2-piperidin-4-yl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one hydrochloride

Prepared from (cis)-2-(2,3-Dihydro-2,2-dimethyl-7-methoxybenzofuran-4 carbonyl)-1,2,3,6-tetrahydrobenzoic acid (starting compound A9) in 1-propanol as described for compound A1. After evaporating the solvent, the residue is partitioned between dichloromethane and aqueous sodium carbonate. The dichloromethane layer is dried over magnesium sulfate and evaporated. The residue is dissolved in dichloromethane and after the addition of a solution of hydrochloric acid in ether, the compound precipitates. M. p. 288-290°C

A4. Piperidin-4-yl-hydrazine dihydrochloride

A mixture of 0.1 mole of 4-(N'-tert-Butoxycarbonyl-hydrazino)-piperidine-1-carboxylic acid tert-butyl ester (starting compound A5) and 150 ml of concentrated hydrochloric acid is heated at 90°C for 60 min after which the clear solution is evaporated. The residue is washed with tetrahydrofuran, filtered off and dried under vacuum. M. p. 256-259°C

A5. 4-(N'-tert-Butoxycarbonyl-hydrazino)-piperidine-1-carboxylic acid tert-butyl ester

150 ml of a solution of borohydride in tetrahydrofuran (1.0 mol/l) is slowly added to a solution of 0.12 mole of 4-(tert-Butoxycarbonyl-hydrazono)-piperidine-1-carboxylic acid tert-butyl ester (starting compound A6) in 100 ml of dry tetrahydrofuran. After complete addition, the mixture is stirred for another 30 min after which a 100 ml of water is added to destroy the excess of borohydride. Subsequently the

tetrahydrofurane is evaporated and the resulting aqueous solution extracted with diethyl ether. After drying the solvent over magnesium sulfate, the ether is evaporated. M. p. 112-115°C

A6. 4-(tert-Butoxycarbonyl-hydrazono)-piperidine-1-carboxylic acid tert-butyl ester

A mixture of 0.15 mole of 4-oxo-piperidine-1-carboxylic acid tert-butyl ester (commercially available) and 0.15 mole of tert-butylcarbrazate in 250 ml of hexane is stirred for 18 h at RT. The precipitate is filtered off and dried under vacuum. M. p. 172-174°C

A7. (cis)-2-(3,4-Dimethoxybenzoyl)-1,2,3,6-tetrahydrobenzoic acid

Prepared as described in WO98/31674.

A8. (cis)-2-(3,4-diethoxybenzoyl)-1,2,3,6-tetrahydrobenzoic acid

Prepared as described in WO99/47505.

A9. (cis)-2-(2,3-Dihydro-2,2-dimethyl-7-methoxybenzofuran-4-carbonyl)-1,2,3,6-tetrahydro-benzolc acid

Prepared as described in WO99/31090.

A10. 6-(3,4-Dimethoxy-phenyl)-5-methyl-2-piperidin-4-yl-4,5-dihydro-2H-pyridazin-3-one hydro-chloride

A mixture of 50 mmol of starting compound A4, 50 mmol of starting compound A13 and 100 mmol of triethylamine in 100 ml of 1-propanol is refluxed for 18 h and subsequently evaporated. The residue is partitioned between dichloromethane and aqueous sodium carbonate. The dichloromethane solution is dried over magnesium sulfate. Addition of a saturated solution of hydrochloric acid in diethyl ether causes precipitation of the title compound. M. p. 91-95°C

A11. 6-(3,4-Dimethoxy-phenyl)-2-piperidin-4-yl-4,5-dihydro-2H-pyridazin-3-one hydrochloride

Prepared as described for starting compound A10 from starting compounds A4 and A14. M. p. 227-229°C

A12. 6-(7-Methoxy-2,2-dimethyl-2,3-dihydro-benzofuran-4-yl)-2-piperidin-4-yl-4,5-dihydro-2H-pyridazin-3-one hydrochloride

Prepared as described for starting compound A10 from starting compounds A4 and A15. M. p. 280°C (with decomposition)

A13. 4-(3,4-Dimethoxy-phenyl)-3-methyl-4-oxo-butyric acid

Prepared according to Haworth and Woodcock; J. Chem. Soc. 1938, 809-811

A14. 4-(3,4-Dimethoxy-phenyl)-4-oxo-butyric acid

Prepared according to M.S.Y. Khan and Anees A. Siddiqui; Indian J. Chem. Section B, 2000, 39, 614-619

A15. 4-(7-Methoxy-2,2-dimethyl-2,3-dihydro-benzofuran-4-yl)-4-oxo-butyric acid

Prepared analogously to (cis)-2-(2,3-Dihydro-7-methoxybenzofuran-2-spiro-1'-cyclopentane-4-carbonyl)-1,2,3,6-tetrahydrobenzoic acid as described in WO99/31090 starting from 4-bromo-7-methoxy-2,2-dimethyl-2,3-dihydro-benzofuran and succinic anhydride. M. p. 125-126°C

A16. (2-oxo-1,2-dihydro-quinolin-6-yloxy)-acetic acid

Prepared as described in T. Nishi, F. Tabusa, T. Tanaka, T. Shimizu, T. Kanbe, Y. Kimura and K. Nakagawa; Chem. Pharm. Bull. 1983, 31, 852-860.

A17. 4-(2-oxo-1,2-dihydro-quinolin-6-yloxy)-butyric acid

Prepared as described in T. Nishi, F. Tabusa, T. Tanaka, T. Shimizu, T. Kanbe, Y. Kimura and K. Nakagawa; Chem. Pharm. Bull. 1983, 31, 852-860.

A18. (4aS,8aR)-2-{1-[3-(2-amino-ethanesulfonyl)-propanoyl]-piperidin-4-yl}-4-(3,4-dimethoxy-phenyl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

Prepared as described in WO01/94319.

A19. (cis)-2-(2,3-Dihydro-7-methoxybenzofuran-2-spiro-1'-cyclopentane-4-carbonyl)-cyclohexancarboxylic acid

Prepared as described in WO99/31090.

Commercial utility

The compounds according to the invention have useful pharmacological properties which make them industrially utilizable. As selective cyclic nucleotide phosphodiesterase (PDE) inhibitors (specifically of type 4), they are suitable on the one hand as bronchial therapeutics (for the treatment of airway obstructions on account of their dilating action but also on account of their respiratory rate- or respiratory drive-increasing action) and for the removal of erectile dysfunction on account of their vascular dilating action, but on the other hand especially for the treatment of disorders, in particular of an inflammatory nature, e.g. of the airways (asthma prophylaxis), of the skin, of the intestine, of the eyes, of the CNS and of the joints, which are mediated by mediators such as histamine, PAF (platelet-activating factor), arachidonic acid derivatives such as leukotrienes and prostaglandins, cytokines, interleukins, chemokines, alpha-, beta- and gamma-interferon, tumor necrosis factor (TNF) or oxygen free radicals and proteases. In this context, the compounds according to the invention are distinguished by a low toxicity, a good enteral absorption (high bioavailability), a large therapeutic breadth and the absence of significant side effects.

On account of their PDE-inhibiting properties, the compounds according to the invention can be employed in human and veterinary medicine as therapeutics, where they can be used, for example, for the treatment and prophylaxis of the following illnesses: acute and chronic (in particular inflammatory and allergen-induced) airway disorders of varying origin (bronchitis, allergic bronchitis, bronchial asthma, emphysema, COPD); dermatoses (especially of proliferative, inflammatory and allergic type) such as psoriasis (vulgaris), toxic and allergic contact eczema, atopic eczema, seborrheic eczema, Lichen simplex, sunburn, pruritus in the anogenital area, alopecia areata, hypertrophic scars, discoid lupus erythematosus, follicular and widespread pyodermias, endogenous and exogenous acne, acne rosacea and other proliferative, inflammatory and allergic skin disorders; disorders which are based on an excessive release of TNF and leukotrienes, for example disorders of the arthritis type (rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis and other arthritic conditions), disorders of the immune system (AIDS, multiple sclerosis), graft versus host reaction, allograft rejections, types of shock (septic shock, endotoxin shock, gram-negative sepsis, toxic shock syndrome and ARDS (adult respiratory distress syndrome)) and also generalized inflammations in the gastrointestinal region (Crohn's disease and ulcerative colitis); disorders which are based on allergic and/or chronic, immunological false reactions in the region of the upper airways (pharynx, nose) and the adjacent regions (paranasal sinuses, eyes), such as allergic rhinitis/sinusitis, chronic rhinitis/sinusitis, allergic conjunctivitis and also nasal polyps; but also disorders of the heart which can be treated by PDE inhibitors, such as cardiac insufficiency, or disorders which can be treated on account of the tissue-relaxant action of the PDE inhibitors, such as, for example, erectile dysfunction or colics of the kidneys and of the ureters in connection with kidney stones. In addition, the compounds of the invention are useful in the treatment of diabetes insipidus and conditions associated with cerebral metabolic inhibition, such as cerebral senility, senile dementia (Alzheimer's disease), memory impairment associated with Parkinson's disease or multinfarct dementia; and also illnesses of the central nervous system, such as depressions or arteriosclerotic dementia.

The invention further relates to a method for the treatment of mammals, including humans, which are suffering from one of the above mentioned illnesses. The method is characterized in that a therapeutically active and pharmacologically effective and tolerable amount of one or more of the compounds according to the invention is administered to the ill mammal.

The invention further relates to the compounds according to the invention for use in the treatment and/or prophylaxis of illnesses, especially the illnesses mentioned.

The invention also relates to the use of the compounds according to the invention for the production of pharmaceutical compositions which are employed for the treatment and/or prophylaxis of the illnesses mentioned.

The invention furthermore relates to pharmaceutical compositions for the treatment and/or prophylaxis of the illnesses mentioned, which contain one or more of the compounds according to the invention.

Additionally, the invention relates to an article of manufacture, which comprises packaging material and a pharmaceutical agent contained within said packaging material, wherein the pharmaceutical agent is therapeutically effective for antagonizing the effects of the cyclic nucleotide phosphodiesterase of type 4 (PDE4), ameliorating the symptoms of an PDE4-mediated disorder, and wherein the packaging material comprises a label or package insert which indicates that the pharmaceutical agent is useful for preventing or treating PDE4-mediated disorders, and wherein said pharmaceutical agent comprises one or more compounds of formula 1 according to the invention. The packaging material, label and package insert otherwise parallel or resemble what is generally regarded as standard packaging material, labels and package inserts for pharmaceuticals having related utilities.

The pharmaceutical compositions are prepared by processes which are known per se and familiar to the person skilled in the art. As pharmaceutical compositions, the compounds according to the invention (= active compounds) are either employed as such, or preferably in combination with suitable pharmaceutical auxiliaries and/or excipients, e.g. in the form of tablets, coated tablets, capsules, caplets, suppositories, patches (e.g. as TTS), emulsions, suspensions, gels or solutions, the active compound content advantageously being between 0.1 and 95% and where, by the appropriate choice of the auxiliaries and/or excipients, a pharmaceutical administration form (e.g. a delayed release form or an enteric form) exactly suited to the active compound and/or to the desired onset of action can be achieved.

The person skilled in the art is familiar with auxiliaries or excipients which are suitable for the desired pharmaceutical formulations on account of his/her expert knowledge. In addition to solvents, gel formers, ointment bases and other active compound excipients, for example antioxidants, dispersants,

emulsifiers, preservatives, solubilizers, colorants, complexing agents or permeation promoters, can be used.

The administration of the pharmaceutical compositions according to the invention may be performed in any of the generally accepted modes of administration available in the art. Illustrative examples of suitable modes of administration include intravenous, oral, nasal, parenteral, topical, transdermal and rectal delivery. Oral delivery is preferred.

For the treatment of disorders of the respiratory tract, the compounds according to the invention are preferably also administered by inhalation in the form of an aerosol; the aerosol particles of solid, liquid or mixed composition preferably having a diameter of 0.5 to 10 μm , advantageously of 2 to 6 μm .

Aerosol generation can be carried out, for example, by pressure-driven jet atomizers or ultrasonic atomizers, but advantageously by propellant-driven metered aerosols or propellant-free administration of micronized active compounds from inhalation capsules.

Depending on the inhaler system used, in addition to the active compounds the administration forms additionally contain the required excipients, such as, for example, propellants (e.g. Frigen in the case of metered aerosols), surface-active substances, emulsifiers, stabilizers, preservatives, flavorings, fillers (e.g. lactose in the case of powder inhalers) or, if appropriate, further active compounds.

For the purposes of inhalation, a large number of apparatuses are available with which aerosols of optimum particle size can be generated and administered, using an inhalation technique which is as right as possible for the patient. In addition to the use of adaptors (spacers, expanders) and pear-shaped containers (e.g. Nebulator®, Volumatic®), and automatic devices emitting a puffer spray (Autohaler®), for metered aerosols, in particular in the case of powder inhalers, a number of technical solutions are available (e.g. Diskhaler®, Rotadisk®, Turbohaler® or the inhaler described in European Patent Application EP 0 505 321), using which an optimal administration of active compound can be achieved.

For the treatment of dermatoses, the compounds according to the invention are in particular administered in the form of those pharmaceutical compositions which are suitable for topical application. For the production of the pharmaceutical compositions, the compounds according to the invention (= active compounds) are preferably mixed with suitable pharmaceutical auxiliaries and further processed to give suitable pharmaceutical formulations. Suitable pharmaceutical formulations are, for example, powders, emulsions, suspensions, sprays, oils, ointments, fatty ointments, creams, pastes, gels or solutions.

The pharmaceutical compositions according to the invention are prepared by processes known per se. The dosage of the active compounds is carried out in the order of magnitude customary for PDE inhibitors. Topical application forms (such as ointments) for the treatment of dermatoses thus contain the active compounds in a concentration of, for example, 0.1-99%. The dose for administration by inhala-

tion is customarily between 0.1 and 3 mg per day. The customary dose in the case of systemic therapy (p.o. or i.v.) is between 0.03 and 3 mg/kg per day.

Biological investigations

The second messenger cyclic AMP (cAMP) is well-known for inhibiting inflammatory and immunocompetent cells. The PDE4 isoenzyme is broadly expressed in cells involved in the initiation and propagation of inflammatory diseases (H Tenor and C Schudt, in „Phosphodiesterase Inhibitors“, 21-40, „The Handbook of Immunopharmacology“, Academic Press, 1996), and its inhibition leads to an increase of the intracellular cAMP concentration and thus to the inhibition of cellular activation (JE Souness et al., Immunopharmacology 47: 127-162, 2000).

The antiinflammatory potential of PDE4 inhibitors in vivo in various animal models has been described (MM Teixeira, TiPS 18: 164-170, 1997). For the investigation of PDE4 inhibition on the cellular level (in vitro), a large variety of proinflammatory responses can be measured. Examples are the superoxide production of neutrophilic (C Schudt et al., Arch Pharmacol 344: 682-690, 1991) or eosinophilic (A Hatzelmann et al., Brit J Pharmacol 114: 821-831, 1995) granulocytes, which can be measured as luminol-enhanced chemiluminescence, or the synthesis of tumor necrosis factor- α in monocytes, macrophages or dendritic cells (Gantner et al., Brit J Pharmacol 121: 221-231, 1997, and Pulmonary Pharmacol Therap 12: 377-386, 1999). In addition, the immunomodulatory potential of PDE4 inhibitors is evident from the inhibition of T-cell responses like cytokine synthesis or proliferation (DM Essayan, Biochem Pharmacol 57: 965-973, 1999). Substances which inhibit the secretion of the afore-mentioned proinflammatory mediators are those which inhibit PDE4. PDE4 inhibition by the compounds according to the invention is thus a central indicator for the suppression of inflammatory processes.

Method for measuring inhibition of PDE4 activity

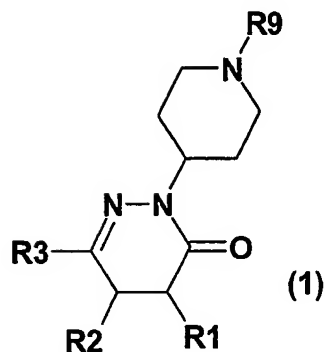
PDE4 activity was determined as described by Thompson et al. (Adv Cycl Nucl Res 10: 69-92, 1979) with some modifications (Bauer and Schwabe, Naunyn-Schmiedeberg's Arch Pharmacol 311: 193-198, 1980). At a final assay volume of 200 μ l (96well microtiter plates) the assay mixture contained 20 mM Tris (pH 7.4), 5 mM $MgCl_2$, 0.5 μ M cAMP, [3H]cAMP (about 30,000 cpm/assay), the test compound and an aliquot of cytosol from human neutrophils which mainly contains PDE4 activity as described by Schudt et al. (Naunyn-Schmiedeberg's Arch Pharmacol 344: 682-690, 1991); the PDE3-specific inhibitor Motapizone (1 μ M) was included to suppress PDE3 activity originating from contaminating platelets. Serial dilutions of the compounds were prepared in DMSO and further diluted 1:100 (v/v) in the assays to obtain the desired final concentrations of the inhibitors at a DMSO concentration of 1 % (v/v) which by itself only slightly affected PDE4 activity.

After preincubation for 5 min at 37°C, the reaction was started by the addition of substrate (cAMP) and the assays were incubated for further 15 min at 37°C. 50 μ l of 0.2 N HCl was added to stop the reaction and the assays were left on ice for about 10 min. Following incubation with 25 μ g 5'-nucleotidase (Crotalus atrox snake venom) for 10 min at 37°C, the assays were loaded on QAE Sephadex A-25 (1 ml bed

volume). The columns were eluted with 2 ml of 30 mM ammonium formate (pH 6.0) and the eluate was counted for radioactivity. Results were corrected for blank values (measured in the presence of denatured protein) which were below 5 % of total radioactivity. The amount of cyclic nucleotides hydrolyzed did not exceed 30 % of the original substrate concentration. The IC_{50} -values for the compounds according to the invention for the inhibition of the PDE4 activity were determined from the concentration-inhibition curves by nonlinear-regression.

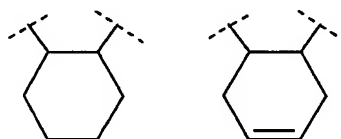
For the following compounds of formula 1 PDE4 inhibitory values [measured as $-\log IC_{50}$ (mol/l)] ≥ 9 were determined. The numbers of the compounds correspond to the numbers of the examples.

Compounds 1-7 and 9-12.

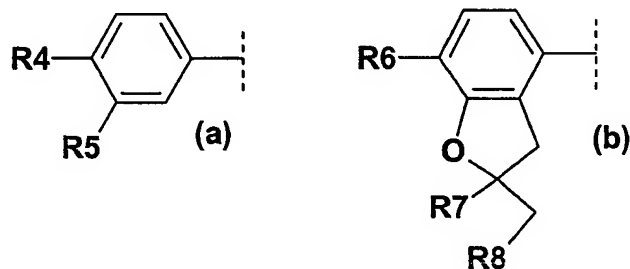
Patent claims**1. Compounds of formula 1**

in which

R1 and R2 represent independently from one another hydrogen or 1-4C-alkyl, or R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,
 R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is 1-4C-alkyl and

R8 is hydrogen or 1-4C-alkyl,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is Aryl1, Aryl2 substituted by R10 and R11, $-(CH_2)_n-C(O)-R12$, $-C(O)-(CH_2)_m-R13$, $-(CH_2)_p-R14$ or $-Y-(CH_2)_q-Z-(CH_2)_r-R16$,

wherein

Aryl1 is naphthyl, pyrazinyl, pyridazinyl, pyrimidin-4-yl, pyrimidin-5-yl, quinazolinyl, quinoxalinyl, cinnolinyl, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl or thiophenyl,

Aryl2 is naphthyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinazolinyl, quinoxalinyl, cinnolinyl, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R10 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylamino-carbonyl,

R11 is hydrogen, halogen, amino, nitro, 1-4C-alkyl or 1-4C-alkoxy,

R12 is 4H-benzo[1,4]oxazin-3-one-6-yl, Aryl2 or Aryl2 substituted by R10 and R11,

R13 is 1-4C-alkoxy, phenoxy, naphthalenoxy or 2-oxo-1,2-dihydro-quinolin-6-yloxy,

R14 is Aryl 3, Aryl2 substituted by R10 and R11, phenyl substituted by R15,

wherein

Aryl3 is naphthyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinazolinyl, quinoxalinyl, cinnolinyl, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R15 is purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R16 is hydrogen, hydroxyl, 1-4C-alkoxy, hydroxy-2-4C-alkoxy, 1-4C-alkoxy-2-4C-alkoxy, mono- or di-1-4C-dialkylamino, 1-4C-alkoxycarbonyl, amino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino or $-N(H)-C(O)-N(R18)R19$,

Y represents a bond or $-C(O)-$,

Z represents a bond, $-O-$, $-C(O)-$, $-C(O)-N(H)-$, $-N(H)-C(O)-$, $-N(R17)-$, $-S-$ or $-S(O)_2-$,

R17 is hydrogen or 1-4C-alkyl,

R18 and R19 are independent from each other hydrogen or 1-4C-alkyl, or R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-, 1-pyrrolidinyl-, 1-piperidinyl-, 1-hexahydroazepino- or a 1-piperazinyl-ring,

n is an integer from 1 to 4,

m is an integer from 1 to 4,

p is an integer from 1 to 4,

q is an integer from 1 to 4,

r is an integer from 1 to 4,

and the salts of these compounds – with the proviso that all those compounds of formula 1 are excluded in which Y and Z both represent a bond and simultaneously R16 is hydrogen, aminocarbonyl or mono- or di-1-4C-alkyl-aminocarbonyl, or in which Y represents –C(O)–, Z represents a bond and simultaneously R16 is hydrogen, amino or mono- or di-1-4C-alkylamino - for use in the treatment of diseases.

2. Compounds of formula 1 according to claim 1 selected from

(4aS,8aR)-2-{1-[3-(2-Amino-ethylsulfanyl)-propanoyl]-piperidin-4-yl}-4-(3,4-dimethoxy-phenyl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one,

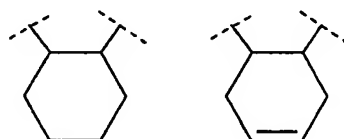
(4aS,8aR)-2-{1-[3-(2-Amino-ethylsulfonyl)-propanoyl]-piperidin-4-yl}-4-(3,4-dimethoxy-phenyl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one,

(4aS,8aR)-2-{1-[2-(2-Amino-ethoxy)-ethyl]-piperidin-4-yl}-4-(3,4-dimethoxy-phenyl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one,

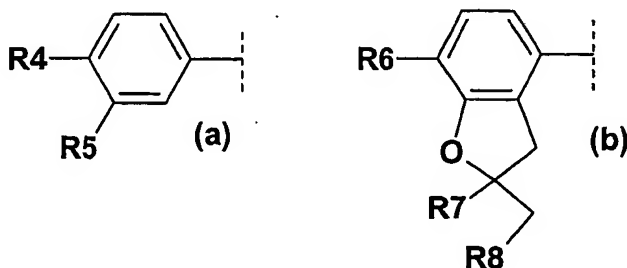
and the salts of these compounds for use in the treatment of diseases.

3. Use of compounds of formula 1 in which

R1 and R2 represent independently from one another hydrogen or 1-4C-alkyl, or R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is 1-4C-alkyl and

R8 is hydrogen or 1-4C-alkyl,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is Aryl1, Aryl2 substituted by R10 and R11, $-(CH_2)_n-C(O)-R12$, $-C(O)-(CH_2)_m-R13$, $-(CH_2)_p-R14$ or $-Y-(CH_2)_q-Z-(CH_2)_r-R16$,

wherein

Aryl1 is naphthyl, pyrazinyl, pyridazinyl, pyrimidin-4-yl, pyrimidin-5-yl, quinazolinyl, quinoxalinyl, cinnolinyl, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl or thiophenyl,

Aryl2 is naphthyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinazolinyl, quinoxalinyl, cinnolinyl, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R10 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylamino-carbonyl,

R11 is hydrogen, halogen, amino, nitro, 1-4C-alkyl or 1-4C-alkoxy,

R12 is 4H-benzo[1,4]oxazin-3-one-6-yl, Aryl2 or Aryl2 substituted by R10 and R11,

R13 is 1-4C-alkoxy, phenoxy, naphthalenoxy or 2-oxo-1,2-dihydro-quinolin-6-yloxy,

R14 is Aryl3, Aryl2 substituted by R10 and R11, phenyl substituted by R15,

wherein

Aryl3 is naphthyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinazolinyl, quinoxalinyl, cinnolinyl, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R15 is purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R16 is hydrogen, hydroxyl, 1-4C-alkoxy, hydroxy-2-4C-alkoxy, 1-4C-alkoxy-2-4C-alkoxy, mono- or di-1-4C-dialkylamino, 1-4C-alkoxycarbonyl, amino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino or $-N(H)-C(O)-N(R18)R19$,

Y represents a bond or $-C(O)-$,

Z represents a bond, $-O-$, $-C(O)-$, $-C(O)-N(H)-$, $-N(H)-C(O)-$, $-N(R17)-$, $-S-$ or $-S(O)_2-$,

R17 is hydrogen or 1-4C-alkyl,

R18 and R19 are independent from each other hydrogen or 1-4C-alkyl, or R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-, 1-pyrrolidinyl-, 1-piperidinyl-, 1-hexahydroazepino- or a 1-piperazinyl-ring,

n is an integer from 1 to 4,

m is an integer from 1 to 4,

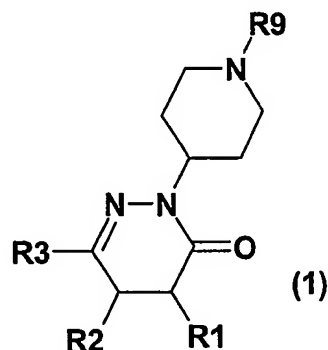
p is an integer from 1 to 4,

q is an integer from 1 to 4,

r is an integer from 1 to 4,

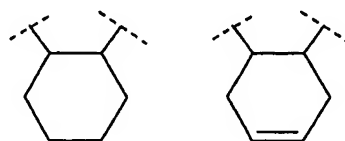
and the salts of these compounds – with the proviso that all those compounds of formula 1 are excluded in which Y and Z both represent a bond and simultaneously R16 is hydrogen, aminocarbonyl or mono- or di-1-4C-alkylaminocarbonyl, or in which Y represents –C(O)-, Z represents a bond and simultaneously R16 is hydrogen; amino or mono- or di-1-4C-alkylamino - for the preparation of pharmaceutical compositions for the treatment of diseases which can be ameliorated by the administration of PDE4 inhibitors.

4. Compounds of formula 1

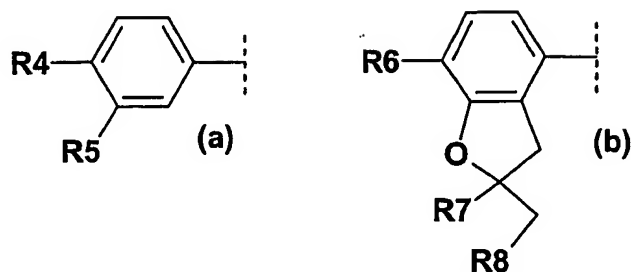


in which

R1 and R2 represent independently from one another hydrogen or 1-4C-alkyl, or R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is 1-4C-alkyl and

R8 is hydrogen or 1-4C-alkyl,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is Aryl1, Aryl2 substituted by R10 and R11, $-(CH_2)_n-C(O)-R12$, $-C(O)-(CH_2)_m-R13$, $-(CH_2)_p-R14$ or $-Y-(CH_2)_q-Z-(CH_2)_r-R16$,

wherein

Aryl1 is naphthyl, pyrazinyl, pyridazinyl, pyrimidin-4-yl, pyrimidin-5-yl, quinazolinyl, quinoxalinyl, cinnolyl, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl or thiophenyl,

Aryl2 is naphthyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinazolinyl, quinoxalinyl, cinnolyl, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R10 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylamino-carbonyl,

R11 is hydrogen, halogen, amino, nitro, 1-4C-alkyl or 1-4C-alkoxy,

R12 is 4H-benzo[1,4]oxazin-3-one-6-yl, Aryl2 or Aryl2 substituted by R10 and R11,

R13 is 1-4C-alkoxy, phenoxy, naphthalenoxy or 2-oxo-1,2-dihydro-quinolin-6-yloxy,

R14 is Aryl 3, Aryl2 substituted by R10 and R11, phenyl substituted by R15,

wherein

Aryl3 is naphthyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinazolinyl, quinoxalinyl, cinnoliny, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R15 is purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R16 is hydrogen, hydroxyl, 1-4C-alkoxy, hydroxy-2-4C-alkoxy, 1-4C-alkoxy-2-4C-alkoxy, mono- or di-1-4C-dialkylamino, 1-4C-alkoxycarbonyl, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino or $-N(H)-C(O)-N(R18)R19$,

Y represents a bond or $-C(O)-$,

Z represents a bond, $-O-$, $-C(O)-$, $-C(O)-N(H)-$, $-N(H)-C(O)-$, $-N(R17)-$, $-S-$ or $-S(O)_2-$,

R17 is hydrogen or 1-4C-alkyl,

R18 and R19 are independent from each other hydrogen or 1-4C-alkyl, or R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-, 1-pyrrolidinyl-, 1-piperidinyl-, 1-hexahydroazepino- or a 1-piperazinyl-ring,

n is an integer from 1 to 4,

m is an integer from 1 to 4,

p is an integer from 1 to 4,

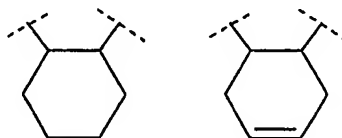
q is an integer from 1 to 4,

r is an integer from 1 to 4,

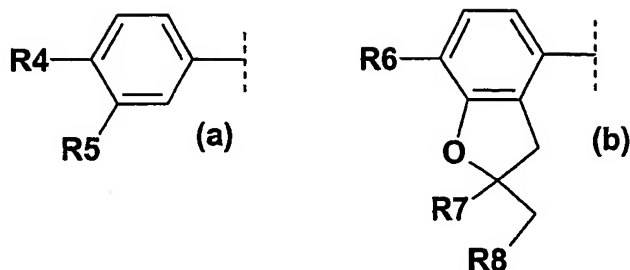
and the salts of these compounds – with the proviso that all those compounds of formula 1 are excluded in which Y and Z both represent a bond and simultaneously R16 is hydrogen, aminocarbonyl or mono- or di-1-4C-alkyl-aminocarbonyl, or in which Y represents $-C(O)-$, Z represents a bond and simultaneously R16 is hydrogen or mono- or $-di-1-4C-alkylamino$.

5. Compounds of formula 1 according to claim 4, in which

R1 and R2 represent independently from one another hydrogen or 1-4C-alkyl, or R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-4C-alkoxy,

R6 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is methyl and

R8 is hydrogen,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane, cyclohexane, tetrahydrofurane or tetrahydropyran ring.

R9 is Aryl1, Aryl2 substituted by R10 and R11, $-(CH_2)_n-C(O)-R12$, $-C(O)-(CH_2)_m-R13$, $-(CH_2)_p-R14$ or $-Y-(CH_2)_q-Z-(CH_2)_r-R16$,

wherein

Aryl1 is pyrimidin-4-yl, pyrimidin-5-yl, quinazolinyl, quinolyl, isoquinolyl, indolyl, indazolyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl or thiophenyl,

Aryl2 is pyridyl, pyrimidinyl, quinazolinyl, quinolyl, isoquinolyl, indolyl, indazolyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R10 is halogen, nitro, cyano, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylaminocarbonyl,

R11 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

R12 is 4H-benzo[1,4]oxazin-3-one-6-yl, Aryl2 or Aryl2 substituted by R10 and R11,

R13 is phenoxy, naphthalenoxy or 2-oxo-1,2-dihydro-quinolin-6-yloxy,

R14 is Aryl 3, Aryl2 substituted by R10 and R11, phenyl substituted by R15,

wherein

Aryl3 is pyrimidinyl, quinazolinyl, quinolyl, isoquinolyl, indolyl, indazolyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R15 is purinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, furanyl or thiophenyl,

Y represents a bond or $-C(O)-$,

Z represents a bond, -O-, -S- or -S(O)₂-,

R16 is hydrogen, hydroxyl, 1-4C-alkoxy, hydroxy-2-4C-alkoxy, 1-4C-alkoxy-2-4C-alkoxy or -N(H)-C(O)-N(R18)R19,

wherein

R18 and R19 are independent from each other hydrogen or 1-4C-alkyl, or R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-, 1-pyrrolidinyl- or 1-piperidinyl -ring,

n is an integer from 1 to 2,

m is an integer from 1 to 3,

p is an integer from 1 to 2,

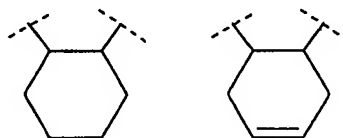
q is an integer from 1 to 3,

r is an integer from 1 to 2,

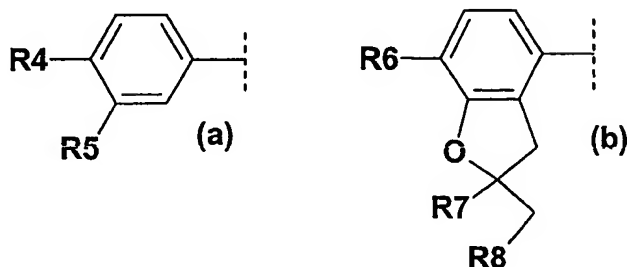
and the salts of these compounds – with the proviso that all those compounds of formula 1 are excluded in which Y and Z both represent a bond and simultaneously R16 is hydrogen, or in which Y represents -C(O)-, Z represents a bond and simultaneously R16 is hydrogen.

6. Compounds of formula 1 according to claim 4 in which

R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a benzene derivative of formulae (a) or (b)



wherein

R4 is 1-2C-alkoxy,

R5 is 1-4C-alkoxy,

R6 is 1-2C-alkoxy,

R7 is methyl and

R8 is hydrogen,

R9 is $-(CH_2)_n-C(O)-R_{12}$, $-C(O)-(CH_2)_m-R_{13}$, $-(CH_2)_p-R_{14}$ or $-Y-(CH_2)_q-Z-(CH_2)_r-R_{16}$,
wherein

R12 is 4H-benzo[1,4]oxazin-3-one-6-yl or benzofuran-2-yl,

R13 is 2-oxo-1,2-dihydro-quinolin-6-yloxy,

R14 is phenyl substituted by R15,

wherein

R15 is benzimidazolyl,

Y represents a bond or $-C(O)-$,

Z represents a bond, $-O-$, $-S-$ or $-S(O)_2-$,

R16 is hydrogen, hydroxyl, methoxy, hydroxyethoxy, methoxyethoxy or $-N(H)-C(O)-N(R_{18})R_{19}$,

wherein

R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded,
form a 4-morpholinyl-ring,

n is 1,

m is an integer from 1 to 3,

p is 1,

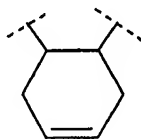
q is an integer from 1 to 2,

r is an integer from 1 to 2,

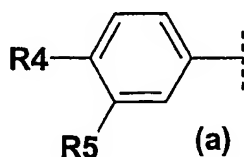
and the salts of these compounds – with the proviso that all those compounds of formula 1 are excluded in which Y and Z both represent a bond and simultaneously R16 is hydrogen, or in which Y represents $-C(O)-$, Z represents a bond and simultaneously R16 is hydrogen.

7. Compounds of formula 1 according to claim 4 in which

R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form the following group



R3 represents a phenyl derivative of formula (a)



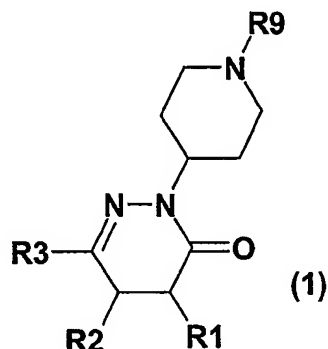
wherein

R4 is methoxy,

R5 is methoxy,

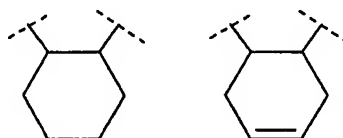
R9 is 2-(methanesulfonyl)ethanoyl, 2-benzofuran-2-yl-2-oxo-ethyl, 4-benzimidazol-1-ylbenzyl, 2-(4H-benzo[1,4]oxazin-3-one-6-yl)ethanoyl, 3-{2-[(1-morpholin-4-yl-methanoyl)-amino]-ethanesulfonyl}-propionyl, 2-(2-oxo-1,2-dihydroquinolin-6-yloxy)ethanoyl, 4-(2-oxo-1,2-dihydroquinolin-6-yloxy)butanoyl, 2-methoxyethyl, 2-methylsulfanylethyl, 2-methanesulfonylethyl or 2-(2-hydroxyethoxy)ethyl, and the salts of these compounds.

8. Compounds of formula 1,

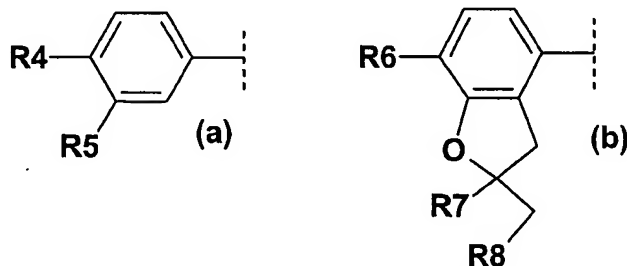


in which

R1 and R2 represent independently from one another hydrogen or 1-4C-alkyl, or R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,
 R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

- R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,
- R7 is 1-4C-alkyl and
- R8 is hydrogen or 1-4C-alkyl,
- or wherein
- R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,
- R9 is Aryl1, Aryl2 substituted by R10 and R11, $-(CH_2)_n-C(O)-R12$, $-C(O)-(CH_2)_m-R13$, $-(CH_2)_p-R14$ or $-Y-(CH_2)_q-Z-(CH_2)_r-R16$,
- wherein
- Aryl1 is naphthyl, pyrazinyl, pyridazinyl, pyrimidin-4-yl, pyrimidin-5-yl, quinazolinyl, quinoxalinyl, cinnolinyl, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl or thiophenyl,
- Aryl2 is naphthyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinazolinyl, quinoxalinyl, cinnolinyl, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,
- R10 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylaminocarbonyl,
- R11 is hydrogen, halogen, amino, nitro, 1-4C-alkyl or 1-4C-alkoxy,
- R12 is 4H-benzo[1,4]oxazin-3-one-6-yl, Aryl2 or Aryl2 substituted by R10 and R11,
- R13 is 1-4C-alkoxy, phenoxy, naphthalenoxy or 2-oxo-1,2-dihydro-quinolin-6-yloxy,
- R14 is Aryl3, Aryl2 substituted by R10 and R11, phenyl substituted by R15,
- wherein
- Aryl3 is naphthyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinazolinyl, quinoxalinyl, cinnolinyl, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,
- R15 is purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,
- R16 is hydrogen, hydroxyl, 1-4C-alkoxy, hydroxy-2-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, mono- or di-1-4C-dialkylamino, 1-4C-alkoxycarbonyl, amino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino or $-N(H)-C(O)-N(R18)R19$,
- Y represents a bond or $-C(O)-$,
- Z represents a bond, $-O-$, $-C(O)-$, $-C(O)-N(H)-$, $-N(H)-C(O)-$, $-N(R17)-$, $-S-$ or $-S(O)_2-$,
- R17 is hydrogen or 1-4C-alkyl,

R18 and R19 are independent from each other hydrogen or 1-4C-alkyl, or R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-, 1-pyrrolidinyl-, 1-piperidinyl-, 1-hexahydroazepino- or a 1-piperazinyl-ring,

n is an integer from 1 to 4,

m is an integer from 1 to 4,

p is an integer from 1 to 4,

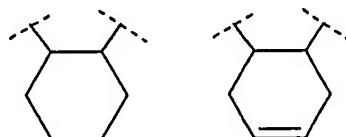
q is an integer from 1 to 4,

r is an integer from 1 to 4,

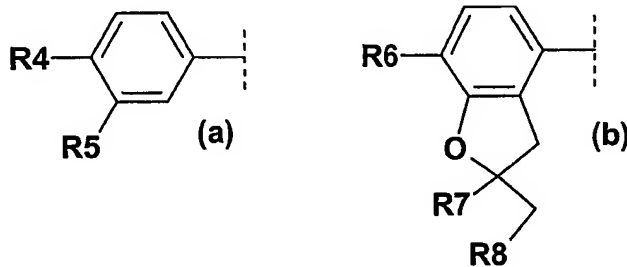
and the salts of these compounds – with the proviso that all those compounds of formula 1 are excluded in which Y and Z both represent a bond and R16 is hydrogen - for use in the treatment of diseases.

9. Use of compounds of formula 1 in which

R1 and R2 represent independently from one another hydrogen or 1-4C-alkyl, or R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is 1-4C-alkyl and

R8 is hydrogen or 1-4C-alkyl,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is Aryl1, Aryl2 substituted by R10 and R11, $-(CH_2)_n-C(O)-R12$, $-C(O)-(CH_2)_m-R13$, $-(CH_2)_p-R14$ or $-Y-(CH_2)_q-Z-(CH_2)_r-R16$,

wherein

Aryl1 is naphthyl, pyrazinyl, pyridazinyl, pyrimidin-4-yl, pyrimidin-5-yl, quinazolinyl, quinoxalinyl, cinnolyl, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl or thiophenyl,

Aryl2 is naphthyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinazolinyl, quinoxalinyl, cinnolyl, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R10 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylamino-carbonyl,

R11 is hydrogen, halogen, amino, nitro, 1-4C-alkyl or 1-4C-alkoxy,

R12 is 4H-benzo[1,4]oxazin-3-one-6-yl, Aryl2 or Aryl2 substituted by R10 and R11,

R13 is 1-4C-alkoxy, phenoxy, naphthalenoxy or 2-oxo-1,2-dihydro-quinolin-6-yloxy,

R14 is Aryl3, Aryl2 substituted by R10 and R11, phenyl substituted by R15,

wherein

Aryl3 is naphthyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinazolinyl, quinoxalinyl, cinnolyl, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R15 is purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R16 is hydrogen, hydroxyl, 1-4C-alkoxy, hydroxy-2-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, mono- or di-1-4C-dialkylamino, 1-4C-alkoxycarbonyl, amino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino or $-N(H)-C(O)-N(R18)R19$,

Y represents a bond or $-C(O)-$,

Z represents a bond, $-O-$, $-C(O)-$, $-C(O)-N(H)-$, $-N(H)-C(O)-$, $-N(R17)-$, $-S-$ or $-S(O)_2-$,

R17 is hydrogen or 1-4C-alkyl,

R18 and R19 are independent from each other hydrogen or 1-4C-alkyl, or R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-, 1-pyrrolidinyl-, 1-piperidinyl-, 1-hexahydroazepino- or a 1-piperazinyl-ring,

n is an integer from 1 to 4,

m is an integer from 1 to 4,

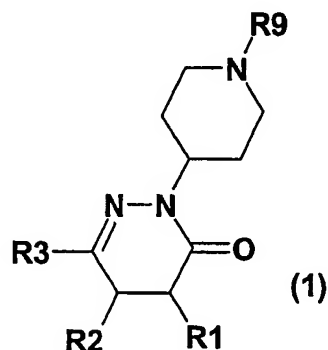
p is an integer from 1 to 4,

q is an integer from 1 to 4,

r is an integer from 1 to 4,

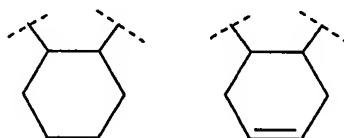
and the salts of these compounds – with the proviso that all those compounds of formula 1 are excluded in which Y and Z both represent a bond and R16 is hydrogen - for the preparation of pharmaceutical compositions for the treatment of diseases which can be ameliorated by the administration of PDE4 inhibitors.

10. Compounds of formula 1

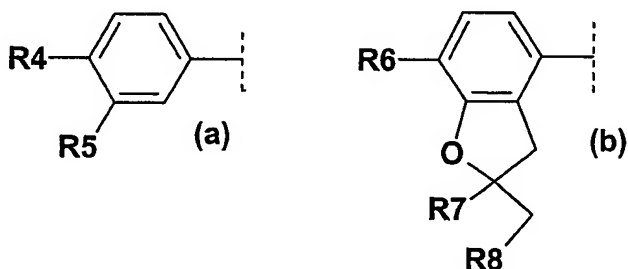


In which

R1 and R2 represent independently from one another hydrogen or 1-4C-alkyl, or R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,
 R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,
 R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is 1-4C-alkyl and

R8 is hydrogen or 1-4C-alkyl,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is Aryl1, Aryl2 substituted by R10 and R11, $-(CH_2)_n-C(O)-R12$, $-C(O)-(CH_2)_m-R13$, $-(CH_2)_p-R14$ or $-Y-(CH_2)_q-Z-(CH_2)_r-R16$,

wherein

Aryl1 is naphthyl, pyrazinyl, pyridazinyl, pyrimidin-4-yl, pyrimidin-5-yl, quinazolinyl, quinoxaliny, cinnoliny, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl or thiophenyl,

Aryl2 is naphthyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinazolinyl, quinoxaliny, cinnoliny, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R10 is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylamino-carbonyl,

R11 is hydrogen, halogen, amino, nitro, 1-4C-alkyl or 1-4C-alkoxy,

R12 is 4H-benzo[1,4]oxazin-3-one-6-yl, Aryl2 or Aryl2 substituted by R10 and R11,

R13 is 1-4C-alkoxy, phenoxy, naphthalenoxy or 2-oxo-1,2-dihydro-quinolin-6-yloxy,

R14 is Aryl 3, Aryl2 substituted by R10 and R11, phenyl substituted by R15,

wherein

Aryl3 is naphthyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinazolinyl, quinoxaliny, cinnoliny, quinolyl, isoquinolyl, phthalazinyl, indanyl, indolyl, isoindolyl, indazolyl, chromanyl, isochromanyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R15 is purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R16 is hydrogen, hydroxyl, 1-4C-alkoxy, hydroxy-2-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, mono- or di-1-4C-dialkylamino, 1-4C-alkoxycarbonyl, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino or $-N(H)-C(O)-N(R18)R19$,

Y represents a bond or $-C(O)-$,

Z represents a bond, $-O-$, $-C(O)-$, $-C(O)-N(H)-$, $-N(H)-C(O)-$, $-N(R17)-$, $-S-$ or $-S(O)_2-$,

R17 is hydrogen or 1-4C-alkyl,

R18 and R19 are independent from each other hydrogen or 1-4C-alkyl, or R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-, 1-pyrrolidinyl-, 1-piperidinyl-, 1-hexahydroazepino- or a 1-piperazinyl-ring,

n is an integer from 1 to 4,

m is an integer from 1 to 4,

p is an integer from 1 to 4,

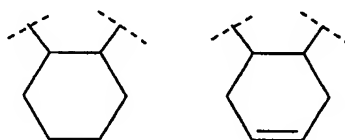
q is an integer from 1 to 4,

r is an integer from 1 to 4,

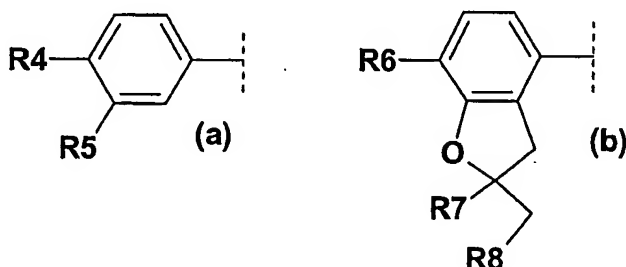
and the salts of these compounds – with the proviso that all those compounds of formula 1 are excluded in which Y and Z both represent a bond and R16 is hydrogen.

11. Compounds of formula 1 according to claim 4 in which

R1 and R2 represent independently from one another hydrogen or 1-4C-alkyl, or R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-4C-alkoxy,

R6 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is methyl and

R8 is hydrogen,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane, cyclohexane, tetrahydrofurane or tetrahydropyran ring,

R9 is Aryl1, Aryl2 substituted by R10 and R11, $-(CH_2)_n-C(O)-R12$, $-C(O)-(CH_2)_m-R13$, $-(CH_2)_p-R14$ or $-Y-(CH_2)_q-Z-(CH_2)_r-R16$,

wherein

Aryl1 is pyrimidin-4-yl, pyrimidin-5-yl, quinazolinyl, quinolyl, isoquinolyl, indolyl, indazolyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl or thiophenyl,

Aryl2 is pyridyl, pyrimidinyl, quinazolinyl, quinolyl, isoquinolyl, indolyl, indazolyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R10 is halogen, nitro, cyano, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkylcarbonylamino or mono- or di-1-4C-alkylaminocarbonyl,

R11 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

R12 is 4H-benzo[1,4]oxazin-3-one-6-yl, Aryl2 or Aryl2 substituted by R10 and R11,

R13 is phenoxy, naphthalenoxy or 2-oxo-1,2-dihydro-quinolin-6-yloxy,

R14 is Aryl3, Aryl2 substituted by R10 and R11, phenyl substituted by R15,

wherein

Aryl3 is pyrimidinyl, quinazolinyl, quinolyl, isoquinolyl, indolyl, indazolyl, purinyl, pteridinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrrolyl, pyrazolyl, furanyl or thiophenyl,

R15 is purinyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, furanyl or thiophenyl,

Y represents a bond or -C(O)-,

Z represents a bond, -O-, -S- or -S(O)₂-,

R16 is hydrogen, hydroxyl, 1-4C-alkoxy, hydroxy-2-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy or -N(H)-C(O)-N(R18)R19,

wherein

R18 and R19 are independent from each other hydrogen or 1-4C-alkyl, or R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-, 1-pyrrolidinyl- or 1-piperidinyl -ring,

n is an integer from 1 to 2,

m is an integer from 1 to 3,

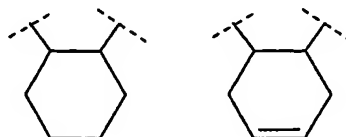
p is an integer from 1 to 2,

q is an integer from 1 to 3,

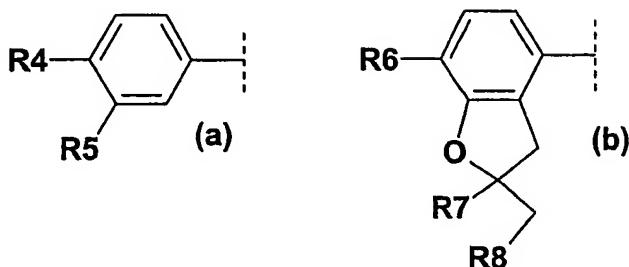
r is an integer from 1 to 2,

and the salts of these compounds – with the proviso that all those compounds of formula 1 are excluded in which Y and Z both represent a bond and R16 is hydrogen.

12. Compounds of formula 1 according to claim 4 in which R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a benzene derivative of formulae (a) or (b)



wherein

R4 is 1-2C-alkoxy,

R5 is 1-4C-alkoxy,

R6 is 1-2C-alkoxy,

R7 is methyl and

R8 is hydrogen,

R9 is $-(CH_2)_n-C(O)-R_{12}$, $-C(O)-(CH_2)_m-R_{13}$, $-(CH_2)_p-R_{14}$ or $-Y-(CH_2)_q-Z-(CH_2)_r-R_{16}$,
wherein

R12 is 4H-benzo[1,4]oxazin-3-one-6-yl or benzofuran-2-yl,

R13 is 2-oxo-1,2-dihydro-quinolin-6-yloxy,

R14 is phenyl substituted by R15,

wherein

R15 is benzimidazolyl,

Y represents a bond or $-C(O)-$,

Z represents a bond, $-O-$, $-S-$ or $-S(O)_2-$,

R16 is hydrogen, hydroxyl, methoxy, hydroxyethoxy, methoxyethoxy or $-N(H)-C(O)-N(R_{18})R_{19}$,
wherein

R18 and R19 together and with inclusion of the nitrogen atom to which they are bonded,
form a 4-morpholinyl-ring,

n is 1,

m is an integer from 1 to 3,

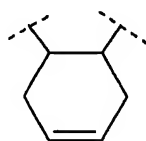
p is 1,

q is an integer from 1 to 3,

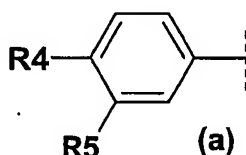
r is an integer from 1 to 2,

and the salts of these compounds – with the proviso that all those compounds of formula 1 are excluded in which Y and Z both represent a bond and R16 is hydrogen.

13. Compounds of formula 1 according to claim 4 in which R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form the following group



R3 represents a phenyl derivative of formula (a)



wherein

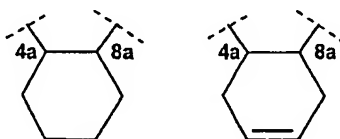
R4 is methoxy,

R5 is methoxy,

R9 is 2-(methanesulfonyl)ethanoyl, 2-benzofuran-2-yl-2-oxo-ethyl, 4-benzimidazol-1-ylbenzyl, 2-(4H-benzo[1,4]oxazin-3-one-6-yl)ethanoyl, 2-(2-oxo-1,2-dihydroquinolin-6-yloxy)ethanoyl, 4-(2-oxo-1,2-dihydroquinolin-6-yloxy)butanoyl, 2-methoxyethyl, 2-methylsulfanylethyl, 2-methanesulfonylethyl or 2-(2-hydroxy-ethoxy)ethyl,

and the salts of these compounds.

14. Compounds of formula 1 according to one of the claims 1 or 3-13, in which R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



and in which the hydrogen atoms in the positions 4a and 8a are cis-configured.

15. Compounds of formula 1 according to claim 14 in which the absolute configuration (according to the rules of Cahn, Ingold and Prelog) is S in the position 4a and R in the position 8a.

16. Compounds of formula 1 according to claim 4 or 10 for the treatment of diseases.
17. Pharmaceutical compositions containing one or more compounds of formula 1 according to claim 4 or 10 together with the usual pharmaceutical auxiliaries and/or carrier materials.
18. Use of compounds of formula 1 according to claim 4 or 10 for the preparation of pharmaceutical compositions for the treatment of airway disorders.
19. A method for treating an illness treatable by the administration of a PDE4 inhibitor in a patient comprising administering to said patient in need thereof a therapeutically effective amount of a compound of formula 1 as claimed in claim 1.
20. A method for treating an illness treatable by the administration of a PDE4 inhibitor in a patient comprising administering to said patient in need thereof a therapeutically effective amount of a compound of formula 1 as claimed in claim 4.
21. A method for treating airway disorders in a patient comprising administering to said patient a therapeutically effective amount of a compound of formula 1 as claimed in claim 1.
22. A method for treating airway disorders in a patient comprising administering to said patient a therapeutically effective amount of a compound of formula 1 as claimed in claim 4.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/08724

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/502 A61K31/50 C07D401/04 C07D401/14 C07D405/14
A61P11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02 085906 A (ALTANA PHARMA AG; STERK GEERT JAN (NL)) 31 October 2002 (2002-10-31) cited in the application Abstract; claims 1-13; example 4. ---	1-22
P,X	WO 02 064584 A (BYK GULDEN LOMBERG CHEM FAB; GUTTERER BEATE (DE); GRUNDLER GERHARD) 22 August 2002 (2002-08-22) cited in the application Abstract; claims 1-14; examples 3,11,12,17,19,21,23,24,27. ---	1-22
	--- -/-	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

13 November 2003

Date of mailing of the international search report

25/11/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Weisbrod, T

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/08724

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 94319 A (BYK GULDEN LOMBERG CHEM FAB; STERK GEERT (NL); BYK NEDERLAND BV (N) 13 December 2001 (2001-12-13) cited in the application	10,14,15
A	Abstract; claims 1-10; intermediates 5a,14a,15a.	1-9, 11-13, 16-22
A	----- WO 98 31674 A (BYK GULDEN LOMBERG CHEM FAB; STERK GEERT JAN (NL)) 23 July 1998 (1998-07-23) Abstract; claims 1-10. -----	1-22

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/08724

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 19-22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/08724

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 02085906	A	31-10-2002	WO 02085906 A2	31-10-2002
WO 02064584	A	22-08-2002	CA 2438520 A1	22-08-2002
			EE 200300311 A	15-10-2003
			WO 02064584 A1	22-08-2002
WO 0194319	A	13-12-2001	AU 6233201 A	17-12-2001
			BR 0111440 A	03-06-2003
			CA 2411351 A1	13-12-2001
			CZ 20023997 A3	14-05-2003
			WO 0194319 A1	13-12-2001
			EP 1296956 A1	02-04-2003
			NO 20025811 A	04-02-2003
			US 2003195215 A1	16-10-2003
WO 9831674	A	23-07-1998	AT 233247 T	15-03-2003
			AU 735934 B2	19-07-2001
			AU 5862998 A	07-08-1998
			BR 9806752 A	14-03-2000
			CN 1249749 T	05-04-2000
			DE 69811645 D1	03-04-2003
			DK 971901 T3	10-06-2003
			EA 2764 B1	29-08-2002
			EE 9900274 A	15-02-2000
			WO 9831674 A1	23-07-1998
			EP 0971901 A1	19-01-2000
			HU 0001541 A2	28-05-2001
			IL 130659 A	25-07-2002
			JP 2001508078 T	19-06-2001
			NO 993301 A	10-09-1999
			NZ 336573 A	27-10-2000
			PL 334561 A1	13-03-2000
			PT 971901 T	31-07-2003
			SI 971901 T1	31-10-2003
			SK 95199 A3	10-12-1999
			TR 9901653 T2	21-10-1999
			US 6103718 A	15-08-2000

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☒ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER: _____**

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.